PA ENT COOPERATION TREAT

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 25 October 2000 (25.10.00)	
International application No. PCT/NZ00/00026	**Applicant's or agent's file reference** P418034 TVG
International filing date (day/month/year) 13 March 2000 (13.03.00)	**Priority date** (day/month/year) 12 March 1999 (12.03.99)
Applicant COOK, Christian, John	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

09 October 2000 (09.10.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

R. E. Stoffel

Telephone No.: (41-22) 338.83.38

0

09/936291

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference P418034 TVG	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. **PCT/NZ00/00026**	International Filing Date *(day/month/year)* 20 April 2000	Priority Date *(day/month/year)* 12 March 1999

International Patent Classification (IPC) or national classification and IPC

Int. Cl. [7] A61K 031/165, A61K 031/44, A61K 031/55, A61K 031/565, A61K 031/57; A61P 025/20, A61P 033/10

Applicant

THE HORTICULTURE AND FOOD RESEARCH INSTITUTE OF NEW ZEALAND LIMITED et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of **5** sheet(s).

3. This report contains indications relating to the following items:

I	[X]	Basis of the report
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[X]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[ ]	Certain observations on the international application

Date of submission of the demand	Date of completion of the report
9 October 2000	9 July 2001
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **MICHAEL GRIEVE** Telephone No. (02) 6283 2267

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/NZ00/00026

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1 to 34**, as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☒ the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages **35 to 37**, received on **22 March 2001** with the letter of **22 March 2001**
pages **38 to 39**, received on **8 May 2001** with the letter of **8 May 2001**

☒ the drawings, pages **1/14 to 14/14**, as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims **1 to 33, 37 to 51**	**YES**
	Claims **34 to 36**	**NO**
Inventive step (IS)	Claims **1 to 33, 37 to 51**	**YES**
	Claims **34 t 36**	**NO**
Industrial applicability (IA)	Claims **1 to 51**	**YES**
	Claims	**NO**

2. Citations and explanations (Rule 70.7)

D1: US 4548813A

D2: AU-A-62943/86

D3: US 5663171A

D4: WO 95/30418A

D5: US 5780220A

D6: US 4576951A

New citations:

D7: US 5643954A (Komissarova, Irina Alexeevna et al.) O.P.I. 1 July 1997

D8: US 5270341A (Keane, Peter-Eugène et al.) O.P.I. 14 December 1993

Please note the documents cited in Box VI

Note:
Rule 67 lists the subject matter which under Article 34(4)(a)(i) an international preliminary examination is not required to be carried out. At item (iv) it specifies methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods, as such matter. However the agreement between WIPO and Australia further qualifies this by excepting from exclusion any subject matter which is examined under national grant procedures. Claims 30 to 41 have nonetheless been considered because the identified subject matter does not contravene Australian law.

Novelty (N)

The present Claims 1 to 51 are considered to be novel over documents D1 to D6, in that these documents do not disclose compositions comprising an antistress agent according to any one of the present Claims 2 to 6 and at least one therapeutic agent selected from anthelmintics, vitamins and amino acids, and methods for promoting production gain in an animal using such compositions.

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
1. P,X US 5937790A	17 August 1999	18 December 1997	18 December 1996
2. P,X WO 99/52379A	21 October 1999	22 March 1999	14 April 1998

1. This document discloses the features of Claims 1, 29 to 31, and 50. See whole document
2. This document discloses the features of Claims 1, 29 to 31, and 50. See whole document

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box V

Claim 34 (and dependent Claims 35 to 36) merely discloses a method for treating stress comprising the administration of at least one antistress agent. This claim is therefore clearly not novel and does not involve an inventive step. This is shown in new documents D7 and D8, where it is known to use antistress agents in a prophylactic manner, and administer antistress agents to aid patients in the recovery from stress associated with illness, injury or trauma.

INVENTIVE STEP (IS)

Claims 34 to 36 - see the comments under novelty above.

CLAIMS:

1. A composition comprising at least one therapeutic agent selected from the group consisting of anthelmintics, vitamins and amino acids, and at least one antistress agent.

2. A composition according to claim 1 wherein the antistress agent is selected from glucocorticoid inhibitors, corticotropin reducing hormone inhibitors, ACTH inhibitors, cholecystokinin inhibitors, benzodiazepines, gamma amino butyric acid potentiators, antiglutaminergics, and serotonergics.

3. A composition according to claim 1 or claim 2 wherein the antistress agent is selected from pyridyl propanones, antiprogestins, benzoylamino dipropylamino oxopentanoics, and amino acid peptides.

4. A composition according to claim 1 wherein the antistress agent is selected from metyrapone, mifepristone, proglumide, astressin, CRH 9-41, diazepam, allopregnanolone, dextromethorpon, zimelidine, and paroxetine.

5. A composition according to claim 4 wherein the antistress agent is selected from metyrapone, mifepristone, proglumide and astressin.

6. A composition according to claim 5 wherein the antistress agent is metyrapone.

7. A composition according to any one of claims 1 to 6 comprising at least two antistress agents, independently selected from the agents according to any one of claims 2 to 6.

8. A composition according to claim 7 wherein the two agents selected are metyrapone and mifepristone, metyrapone and proglumide, or metyrapone and astressin.

9. A composition according to any one of claims 1 to 8 wherein the therapeutic agent is Vitamin C.

10. A composition according to any one of claims 1 to 9 wherein the therapeutic agent further comprises one or more amino acids selected from valine, leucine and isoleucine.

11. A composition according to claim 10 wherein the therapeutic agent comprises valine, leucine and isoleucine.

12. A composition according to any one of claims 1 to 8 wherein the therapeutic agent is an anthelmintic.

13. A composition according to claim 12 which further comprises vitamin C.

14. A composition according to claim 13 which further comprises one or more amino acids selected from valine, leucine and isoleucine.

15. A composition according to claim 14 which further comprises valine, leucine and isoleucine.

16. A composition according to any one of claims 1 to 15 wherein the, or each, antistress agent is present in an amount of from 0.0005 to 1 g/kg of liveweight.

17. A composition according to claim 16 wherein the, or each, antistress agent is present in an amount of from 0.001 to 0.1 g/kg.

18. A composition according to claim 17 wherein the, or each, antistress agent is present in an amount of 0.01 g/kg.

19. A composition according to any one of claims 1 to 18 which further comprises a lipid membrane transfer facilitator.

20. A composition according to claim 19 wherein the facilitator is pyrollopyrimidine.

21. A composition as claimed in any one of claims 1 to 20 which further comprises a performance enhancer.

22. A composition according to claim 21 wherein the performance enhancer is an antibiotic.

23. A composition according to claim 22 wherein the antibiotic is avilamycin.

24. A composition according to claim 22 wherein the performance enhancer is an oligosaccharide.

25. A composition according to claim 24 wherein the oligosaccharide is Bio-Mos.

26. A composition according to any one of claims 1 to 25 which is a slow release composition.

27. A composition according to any one of claims 1 to 26 which further comprises a nitric oxide promoter.

28. A composition according to claim 27 wherein the promoter is selected from L-arginine diethylamine nitric oxide complex, sodium nitroprusside, and S-nitroso-N-acetylpenicillamine.

29. A composition according to any one of claims 1 to 28 which further comprises at least one pharmaceutically or veterinarily acceptable diluent, excipient, carrier or solubiliser.

30. A method for promoting production gain in an animal, the method comprising administering to said animal at least one antistress agent selected from the agents according to any one of claims 2 to 6, or is provided in the form of a composition according to any one of claims 1 to 29.

31. A method for enhancing the efficacy of a therapeutic agent selected from the group consisting of anthelmintics, vitamins and amino acids, the method comprising the co-administration of at least one said therapeutic agent and at least one antistress agent to an animal.

32. A method according to claim 31 wherein the antistress agent is selected from the agents according to any one of claims 2 to 6.

33. A method for promoting production gain in an animal, the method comprising administering at least one therapeutic agent to the animal and reducing the stress experienced by the animal, wherein reduction in stress is achieved by administering at least one antistress agent according to any one of claims 2 to 6.

34. A method for protecting an animal against, or aiding recovery from, stress associated with surgery, injury, illness or trauma, the method comprising administering to said animal at least one antistress agent.

35. A method according to claim 34 wherein the agent is selected from the agents according to any one of claims 2 to 6, or is provided in the form of a composition according to any one of claims 1 to 29, with the proviso that the composition is not an anthelmintic composition.

36. A method according to any one of claims 30 to 35, wherein at least two antistress agents independently selected from the agents according to any one of claims 2 to 6 are administered.

37. A method according to any one of claims 30 to 36 which further comprises administering vitamin C.

38. A method according to any one of claims 30 to 37 which further comprises administering one to three amino acids selected from valine, leucine, and isoleucine.

39. A method according to any one of claims 29 to 38 which further comprises administering a lipid membrane transfer facilitator.

40. A method according to claim 39 wherein the facilitator is pyrollopyrimidine.

41. A method according to any one of claims 30 to 40 wherein the, or each, amino acid is administered in an amount according to any one of claims 16 to 18.

42. A composition comprising a therapeutic agent and a nitric oxide promoter.

43. A composition according to claim 42 wherein the promoter is selected from S-nitroso-N-acetylpenicillamine, sodium nitroprusside and L-arginine diethylamine nitric oxide complex.

44. A composition according to claim 42 or claim 43 wherein the therapeutic agent is an anthelmintic.

45. A composition as claimed in any one of claims 1 to 29 and 42 to 44 which is a drench.

46. A composition as claimed in claim 44 which is a pour-on formulation.

47. A composition as claimed in claim 44 which is formulated for injection.

48. A composition as claimed in claim 44 which is an animal feedstuff.

49. A composition as claimed in claim 44 which is in the form of a bolus.

50. Use of an antistress agent in the production of a composition for use in promoting production gain in an animal wherein the composition comprising the antistress agent is an anthelmintic, vitamin or amino acid composition.

51. Use according to claim 44 wherein the antistress agent is selected from the agent according to any one of claims 2 to 6.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P418034 TVG	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. **PCT/NZ00/00026**	International Filing Date *(day/month/year)* 20 April 2000	Priority Date *(day/month/year)* 12 March 1999
International Patent Classification (IPC) or national classification and IPC **Int. Cl.** [7] A61K 031/165, A61K 031/44, A61K 031/55, A61K 031/565, A61K 031/57; A61P 025/20, A61P 033/10		
Applicant THE HORTICULTURE AND FOOD RESEARCH INSTITUTE OF NEW ZEALANDLIMITED et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of **5** sheet(s).

3. This report contains indications relating to the following items:

I	[X]	Basis of the report
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[X]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[ ]	Certain observations on the international application

Date of submission of the demand 9 October 2000	Date of completion of the report 9 July 2001
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer  **MICHAEL GRIEVE** Telephone No. (02) 6283 2267

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/NZ00/00026

I. Basis of the report

1. With regard to the **elements** of the international application:*

- [ ] the international application as originally filed.
- [X] the description, pages **1 to 34**, as originally filed,
  pages , filed with the demand,
  pages , received on with the letter of
- [X] the claims, pages , as originally filed,
  pages , as amended (together with any statement) under Article 19,
  pages , filed with the demand,
  pages **35 to 37**, received on **22 March 2001** with the letter of **22 March 2001**
  pages **38 to 39**, received on **8 May 2001** with the letter of **8 May 2001**
- [X] the drawings, pages **1/14 to 14/14**, as originally filed,
  pages , filed with the demand,
  pages , received on with the letter of
- [ ] the sequence listing part of the description:
  pages , as originally filed
  pages , filed with the demand
  pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

- [ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- [ ] the language of publication of the international application (under Rule 48.3(b)).
- [ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- [ ] contained in the international application in written form.
- [ ] filed together with the international application in computer readable form.
- [ ] furnished subsequently to this Authority in written form.
- [ ] furnished subsequently to this Authority in computer readable form.
- [ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- [ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. [ ] The amendments have resulted in the cancellation of:
   - [ ] the description, pages
   - [ ] the claims, Nos.
   - [ ] the drawings, sheets/fig.

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims **1 to 33, 37 to 51**	**YES**
	Claims **34 to 36**	**NO**
Inventive step (IS)	Claims **1 to 33, 37 to 51**	**YES**
	Claims **34 t 36**	**NO**
Industrial applicability (IA)	Claims **1 to 51**	**YES**
	Claims	**NO**

2. Citations and explanations (Rule 70.7)

D1: US 4548813A

D2: AU-A-62943/86

D3: US 5663171A

D4: WO 95/30418A

D5: US 5780220A

D6: US 4576951A

New citations:

D7: US 5643954A (Komissarova, Irina Alexeevna et al.) O.P.I. 1 July 1997

D8: US 5270341A (Keane, Peter-Eugène et al.) O.P.I. 14 December 1993

Please note the documents cited in Box VI

Note:
Rule 67 lists the subject matter which under Article 34(4)(a)(i) an international preliminary examination is not required to be carried out. At item (iv) it specifies methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods, as such matter. However the agreement between WIPO and Australia further qualifies this by excepting from exclusion any subject matter which is examined under national grant procedures. Claims 30 to 41 have nonetheless been considered because the identified subject matter does not contravene Australian law.

Novelty (N)

The present Claims 1 to 51 are considered to be novel over documents D1 to D6, in that these documents do not disclose compositions comprising an antistress agent according to any one of the present Claims 2 to 6 and at least one therapeutic agent selected from anthelmintics, vitamins and amino acids, and methods for promoting production gain in an animal using such compositions.

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
1. P,X US 5937790A	17 August 1999	18 December 1997	18 December 1996
2. P,X WO 99/52379A	21 October 1999	22 March 1999	14 April 1998

1. This document discloses the features of Claims 1, 29 to 31, and 50. See whole document

2. This document discloses the features of Claims 1, 29 to 31, and 50. See whole document

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box V

Claim 34 (and dependent Claims 35 to 36) merely discloses a method for treating stress comprising the administration of at least one antistress agent. This claim is therefore clearly not novel and does not involve an inventive step. This is shown in new documents D7 and D8, where it is known to use antistress agents in a prophylactic manner, and administer antistress agents to aid patients in the recovery from stress associated with illness, injury or trauma.

INVENTIVE STEP (IS)

Claims 34 to 36 - see the comments under novelty above.

CLAIMS:

1. A composition comprising at least one therapeutic agent and at least one antistress agent.

2. A composition according to claim 1 wherein the therapeutic agent is selected from the group consisting of vaccines, antibiotics, anthelmintics, anti-pathogenic agents, growth promoters, performance enhancers, vitamin, amino acids, and mineral supplements.

3. A composition according to claim 2 wherein the therapeutic agent is an anthelmintic.

4. A composition according to any one of claims 1 to 3 wherein the antistress agent is selected from glucocorticoid inhibitors, corticotropin reducing hormone inhibitors, ACTH inhibitors, cholecystokinin inhibitors, benzodiazepines, gamma amino butyric acid potentiators, antiglutaminergics, and serotonergics.

5. A composition according to any one of claims 1 to 3 wherein the antistress agent is selected from pyridyl propanones, antiprogestins, benzoylamino dipropylamino oxopentanoics, and amino acid peptides.

6. A composition according to any one of claims 1 to 3 wherein the antistress agent is selected from metyrapone, mifepristone, proglumide, astressin, CRH 9-41, diazepam, allopregnanolone, dextromethorpon, zimelidine, and paroxetine.

7. A composition according to claim 6 wherein the antistress agent is selected from metyrapone, mifepristone, proglumide and astressin.

8. A composition according to claim 6 wherein the antistress agent is metyrapone.

9. A composition according to any one of claims 1 to 8 comprising at least two antistress agents, independently selected from the agents according to any one of claims 4 to 8.

10. A composition according to claim 9 wherein the two agents selected are metyrapone and mifepristone, metyrapone and proglumide, or metyrapone and

astressin.

11. A composition according to any one of claims 1 to 10 which further comprises vitamin C.

12. A composition according to any one of claims 1 to 11 which further comprises one or more amino acids selected from valine, leucine and isoleucine.

13. A composition according to any one of claims 1 to 12 which further comprises valine, leucine and isoleucine.

14. A composition according to any one of claims 1 to 13 wherein the, or each, antistress agent is present in an amount of from 0.0005 to 1 g/kg of liveweight.

15. A composition according to claim 14 wherein the, or each, antistress agent is present in an amount of from 0.001 to 0.1 g/kg.

16. A composition according to claim 15 wherein the, or each, antistress agent is present in an amount of 0.01 g/kg.

17. A composition according to any one of claims 1 to 16 which further comprises a lipid membrane transfer facilitator.

18. A composition according to claim 17 wherein the facilitator is pyrollopyrimidine.

19. A composition as claimed in any one of claims 1 to 18 which further comprises a performance enhancer.

20. A composition according to claim 19 wherein the performance enhancer is an antibiotic.

21. A composition according to claim 19 wherein the performance enhancer is an oligosaccharide.

22. A composition according to any one of claims 1 to 21 which is a slow release composition.

23. A composition according to any one of claims 1 to 22 which further comprises at least one pharmaceutically or veterinarily acceptable diluent, excipient, carrier or solubiliser.

24. A method for promoting production gain in an animal, the method comprising administering to said animal at least one antistress agent.

25. A method according to claim 24 wherein the antistress agent is selected from the agents according to any one of claims 4 to 8.

26. A method for enhancing the efficacy of a therapeutic agent, the method comprising the co-administration of at least one therapeutic agent and at least one antistress agent to an animal.

27. A method according to claim 26 wherein the therapeutic agent is an agent according to any one of claims 4 to 8.

28. A method for promoting production gain in an animal, the method comprising administering at least one therapeutic agent to the animal and reducing the stress experienced by the animal.

29. A method according to claim 28 wherein the reduction stress is achieved by reducing physical stress to the animal.

30. A method according to claim 29 wherein reduction in stress is achieved by administering at least one antistress agent according to any one of claims 4 to 8.

31. A method according to any one of claims 24, 25, 26, 28, or 28 to 30, wherein at least two antistress agents independently selected from the agents according to any one of claims 4 to 8 are administered.

32. A method according to any one of claims 24 to 31 which further comprises administering vitamin C.

33. A method according to any one of claims 24 to 32 which further comprises administering one to three amino acids selected from valine, leucine, and isoleucine.

34. A method according to any one of claims 24 to 33 which further comprises administering a lipid membrane transfer facilitator.

35. A method according to claim 34 wherein the facilitator is pyrollopyrimidine.

36. A method according to any one of claims 24 to 35 wherein the, or each, amino acid is administered in an amount according to any one of claims 14 to 16.

37. A composition comprising a therapeutic agent and a nitric oxide promoter.

38. A composition according to claim 37 wherein the promoter is S-nitroso-N-acetylpenicillamine.

39. A composition according to claim 37 or claim 38 wherein the therapeutic agent is an anthelmintic.

40. Use of an antistress agent as an adjuvant for therapeutic agents or compositions.

41. Use of an antistress agent as a promoter of production gain in an animal.

42. Use of an antistress agent in the production of a composition for use in promoting production gain in an animal.

43. Use according to claim 42 wherein the composition is a vaccine, antibiotic, anthelmintic, anti-pathogenic, growth promoter, performance enhancer, vitamin, amino acid or mineral supplement composition.

44. Use according to any one of claims 40 to 43 wherein the antistress agent is selected from the agent according to any one of claims 4 to 8.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ00/00026

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61K 031/165; A61K 031/44; A61K 031/55; A61K 031/565; A61K 031/57; A61P 025/20; A61P 033/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: A61K, SEARCH TERMS AS BELOW

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC AS ABOVE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT; ESpace; PubMed: (stress OR antistress OR metapyrone OR mifepristone OR progulmide OR astressin) AND (animal OR sheep OR cattle OR bovine OR mammal) AND (weight OR production) AND anthelmintic

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,548,813A (LAWSON, Rommon L.) 22 October 1985 See whole document	1-2, 14-16, 23-24, 26-29, 37, 40-43
P,X	US 5,937,790A (ITU et al.) 17 August 1999 See whole document	1-2, 14-16, 23-24, 26-29, 37, 40-43
X	AU-A-62943/86 (Cetus Corporation) 26 March 1987 See whole document	1-2, 14-16, 23-24, 26-29, 37, 40-43

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
15 June 2000

Date of mailing of the international search report
27 JUN 2000

Name and mailing address of the ISA/AU

AUSTRALIAN PATENT OFFICE
PO BOX 200, WODEN ACT 2606, AUSTRALIA
E-mail address: pct@ipaustralia.gov.au
Facsimile No. (02) 6285 3929

Authorized officer

MICHAEL GRIEVE
Telephone No : (02) 6283 2267

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ00/00026

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,663,171A (CHEN et al.) 2 September 1997 See whole document	1-2, 14-16, 23-24, 26-29, 37, 40-43
P,X	WO99/52379A (Solutia Inc.) 21 October 1999 See whole document	1-2, 14-16, 23-24, 26-29, 37, 40-43
X	WO95/30418A (The Johns Hopkins University) 16 November 1995 See whole document	1-2, 4, 6-8, 14-16, 23, 37
X	US 5,780,220A (WEINER et al.) 14 July 1998 See whole document	1-2, 4, 6-7, 14-16, 23, 37
X	US 4,576,951A (ROVATI et al.) 18 March 1986 See whole document	1, 6-7, 11, 14-16, 19, 21-23, 37

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ00/00026

Box I Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos :

because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos : 28-29, 37-39

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The claims as presently drafted are extremely broad and ill defined, and hence were very difficult to search for ISR purposes.

Claim 28 (and its dependent Claim 29) in particular does not appear to define the present invention, in that it is not necessary for an antistress agent to be present - this claim may merely encompass leading the animal patient away from the stressful situation following the administration of a therapeutic agent.

Claim 37 ("a composition comprising a therapeutic agent and a nitric oxide promoter") appears to have merely described the mechanism of action of the antistress agents - they act as nitric oxide promoters in the brain.

As a result of the above, the following inventive concept (as determined by the IS examiner) was searched:

compositions comprising an antistress agent and a therapeutic agent, and the use of such compositions for promoting production/weight gain in an animal.

3. ☐ Claims Nos :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/NZ00/00026

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	4548813	NONE					
US	5937790	EP	848955	JP	10175866		
AU	62943/86	US	4818769	CA	1297003	CN	86106369
		EP	219979	EP	400762	JP	62123129
		US	5102872	US	5100664	US	5503841
		US	5643565	US	5800810	US	6060068
US	5663171	AU	12945/95	CA	2176140	EP	730578
		WO	9514666				
WO	9952379	AU	30122/99	US	6017564		
WO	9530418	AU	24736/95				
US	5780220	AU	25880/95	CA	2190613	EP	759693
		US	5639598	WO	9531901		
US	4576951	DE	3445183	FR	2556216	GB	2151136
		IT	1160131	JP	60197619		

END OF ANNEX

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* P418034 TVG

Box No. I TITLE OF INVENTION

AGENTS AND METHODS FOR PROMOTING PRODUCTION GAINS IN ANIMALS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

THE HORTICULTURE AND FOOD RESEARCH INSTITUTE OF NEW ZEALAND LIMITED
Corporate Office
Private Bag 11030
Palmerston North
New Zealand

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: New Zealand

State *(that is, country)* of residence: New Zealand

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

COOK, Christian John
70 Nevada Road
Hamilton
New Zealand

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: New Zealand

State *(that is, country)* of residence: New Zealand

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☐ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

A J PARK & SON: CALHOUN, Douglas C; CHRISTIE, Andrew L; GRIFFITHS, Teresa V; JONES, David J; MCCN, Kenneth R; SYDDALL, THOMAS H; and THOMSON, Keith C;

all of 6th Floor, Huddart Parker Building, Post Office Square, P O Box 949, Wellington 6015, New Zealand

Telephone No. +64 4 473-8278

Facsimile No. +64 4 472-3358

Teleprinter No.

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☒ AP **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ EA **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ EP **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ OA **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ AE United Arab Emirates
☒ AL Albania
☒ AM Armenia
☒ AT Austria
☒ AU Australia
☒ AZ Azerbaijan
☒ BA Bosnia and Herzegovina
☒ BB Barbados
☒ BG Bulgaria
☒ BR Brazil
☒ BY Belarus
☒ CA Canada
☒ CH and LI Switzerland and Liechtenstein
☒ CN China
☒ CR Costa Rica
☒ CU Cuba
☒ CZ Czech Republic
☒ DE Germany
☒ DK Denmark
☒ DM Dominica
☒ EE Estonia
☒ ES Spain
☒ FI Finland
☒ GB United Kingdom
☒ GD Grenada
☒ GE Georgia
☒ GH Ghana
☒ GM Gambia
☒ HR Croatia
☒ HU Hungary
☒ ID Indonesia
☒ IL Israel
☒ IN India
☒ IS Iceland
☒ JP Japan
☒ KE Kenya
☒ KG Kyrgyzstan
☒ KP Democratic People's Republic of Korea
☒ KR Republic of Korea
☒ KZ Kazakhstan
☒ LC Saint Lucia
☒ LK Sri Lanka
☒ LR Liberia
☒ LS Lesotho
☒ LT Lithuania
☒ LU Luxembourg
☒ LV Latvia
☒ MA Morocco
☒ MD Republic of Moldova
☒ MG Madagascar
☒ MK The former Yugoslav Republic of Macedonia
☒ MN Mongolia
☒ MW Malawi
☒ MX Mexico
☒ NO Norway
☒ NZ New Zealand
☒ PL Poland
☒ PT Portugal
☒ RO Romania
☒ RU Russian Federation
☒ SD Sudan
☒ SE Sweden
☒ SG Singapore
☒ SI Slovenia
☒ SK Slovakia
☒ SL Sierra Leone
☒ TJ Tajikistan
☒ TM Turkmenistan
☒ TR Turkey
☒ TT Trinidad and Tobago
☒ TZ United Republic of Tanzania
☒ UA Ukraine
☒ UG Uganda
☒ US United States of America
☒ UZ Uzbekistan
☒ VN Viet Nam
☒ YU Yugoslavia
☒ ZA South Africa
☒ ZW Zimbabwe

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ DZ Algeria
☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims a[illegible]cated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 12 March 1999 12/03/99	334627	New Zealand		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1)

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)* :

ISA / AU

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	:	3
description (excluding sequence listing part)	:	34
claims	:	4
abstract	:	1
drawings	:	14
sequence listing part of description	:	–
Total number of sheets	:	56

This international application is **accompanied** by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application:

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Teresa V Griffiths
Agent for the Applicant

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET
Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference P418034 TVG

Applicant
THE HORTICULTURE AND FOOD RESEARCH INSTITUTE OF NEW ZEALAND LIMITED

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . $180.00 T

2. SEARCH FEE . . . . . $990.00 S

International search to be carried out by AU (Australian Patent Office)

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 56 sheets.

first 30 sheets $822.00 b1

26 (remaining sheets) x $19.00 (additional amount) = $494.00 b2

Add amounts entered at b1 and b2 and enter total at B . . . . $1316.00 B

Designation Fees

The international application contains 105 designations.

8 (number of designation fees payable *(maximum ~~10~~ 8)*) x $178.00 (amount of designation fee) = $1424.00 D

Add amounts entered at B and D and enter total at I . . . . . $2740.00 I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . - P

5. TOTAL FEES PAYABLE $3910.00

Add amounts entered at T, S, I and P, and enter total in the TOTAL box — TOTAL

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☐ authorization to charge deposit account (see below)	☐ bank draft	☐ coupons
☒ cheque	☐ cash	☐ other *(specify)*:
☐ postal money order	☐ revenue stamps	

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/ _____ ☐ is hereby authorized to charge the total fees indicated above to my deposit account.

☐ *(this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

Deposit Account No. | Date *(day/month/year)* | Signature

See Notes to the fee calculation sheet

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ AU

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference: P418034 TVG
International application No.: PCT/NZ00/00026	International filing date *(day/month/year)*: 13 March 2000	(Earliest) Priority date *(day/month/year)*: 12 March 1999

Title of invention:
AGENTS AND METHODS FOR PROMOTING PRODUCTION GAINS IN ANIMALS

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
THE HORTICULTURE AND FOOD RESEARCH INSTITUTE OF NEW ZEALAND LIMITED
Corporate Office
Private Bag 11030
Palmerston North
New Zealand

Telephone No.:
Facsimile No.:
Teleprinter No.:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
New Zealand	New Zealand

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
COOK, Christian John
70 Nevada Road
Hamilton
New Zealand

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
New Zealand	New Zealand

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on a continuation sheet.

See Notes to the demand form

International application No.
PCT/NZ00/00026

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

A J PARK: CALHOUN, Douglas C; CHRISTIE, Andrew L; GRIFFITHS, Teresa V; JONES, David J; MOON, Kenneth R; SYDDALL, Thomas H; and THOMSON, Keith C;

all of 6th Floor, Huddart Parker Building, Post Office Square, P O Box 949, Wellington 6015, New Zealand

Telephone No.: +64 4 473-8278

Facsimile No.: +64 4 472-3358

Teleprinter No.:

[ ] Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special addr ess to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments: *

1. The applicant wishes the international preliminary examination **to start on the basis of:**

[X] the international application as originally filed

the description [X] as originally filed
[ ] as amended under Article 34

the claims [X] as originally filed
[ ] as amended under Article 19 (together with any accompanying statement)
[ ] as amended under Article 34

the drawings [X] as originally filed
[ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [ ] The applicant wishes the start of the international preliminary examination **to be postponed** until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

[X] which is the language in which the international application was filed.
[ ] which is the language of a translation furnished for the purposes of international search.
[ ] which is the language of publication of the international application.
[ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects **all eligible States** *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes **not to elect:**

Sheet No. 3

International application No.
PCT/NZ00/00026

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. [X] fee calculation sheet
2. [ ] separate signed power of attorney
3. [ ] copy of general power of attorney; reference number, if any:
4. [ ] statement explaining lack of signature
5. [ ] nucleotide and or amino acid sequence listing in computer readable form
6. [ ] other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

TERESA V GRIFFITHS
Agent for the Applicant

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PCT

CHAPTER II

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No. PCT/NZ00/00026

Applicant's or agent's file reference P418034 TVG

For International Preliminary Examining Authority use only

Date stamp of the IPEA

Applicant
THE HORTICULTURE AND FOOD RESEARCH INSTITUTE OF NEW ZEALAND LIMITED

Calculation of prescribed fees

1. Preliminary examination fee ..... AU$450.00 P

2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)* ..... AU$238.00 H

3. Total of prescribed fees
Add the amounts entered at P and H and enter total in the TOTAL box..... AU$688.00
TOTAL

Mode of Payment

- [ ] authorization to charge deposit account with the IPEA (see below)
- [X] cheque
- [ ] postal money order
- [ ] bank draft
- [ ] cash
- [ ] revenue stamps
- [ ] coupons
- [ ] other *(specify)*:

Deposit Account Authorization *(this mode of payment may not be available at all IPEAs)*

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(54) Title: AGENTS AND METHODS FOR PROMOTING PRODUCTION GAINS IN ANIMALS

(57) Abstract

The invention relates to compositions and methods for promoting production gains in animals, and for enhancing the efficacy of therapeutic agents. The gains are achieved through reduction in stress, including through the use of antistress agents. Compositions comprising therapeutic agents such as anthelmintics, and antistress agents are provided.

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AGENTS AND METHODS FOR PROMOTING PRODUCTION GAINS IN ANIMALS

FIELD OF THE INVENTION

This invention relates to methods and compositions for promoting production gains in animals and for enhancing efficacy of therapeutic agents.

BACKGROUND TO THE INVENTION

Animals are susceptible to both external and internal parasitic infection and disease. This is especially true in an agricultural environment where a high concentration of animals means that infection and reinfection can easily occur. Parasitic and disease loads on livestock are known to be responsible for a number of conditions such as poor growth, anaemia, scouring, indigestion, poor feed conversion, depression and premature death. These conditions hamper meat production and quality and have a detrimental economic impact on both the farmers and the industry in general.

In order to address this problem, therapeutic agents including vaccines, antibiotics, anthelmintics (also known as anthelminthics) and other anti-pathogenic agents have been used to control disease and the numbers of parasites in and on livestock. Therapeutic agents come in a number of forms, including drenches, pour-ons, wipe-ons, injectables, oral dosages or slow release compositions and are used to prevent, control or eliminate internal and external parasites and disease. Therapeutic agents and especially vaccines, antibiotics and anthelmintics are now well recognised as essential to healthy livestock growth.

However, therapeutic agents have disadvantages in that targeted organisms have been found to be developing resistance. One method used to tackle the increase in resistance has been to increase the number of doses and amounts of the agents administered to livestock.

It has also been shown that increasing agent use can, in and of itself, cause further resistance to the agents to develop.

As a result of increased agent usage, the costs of achieving the same disease or parasitic control per head of livestock escalate because of both an increase in labour and an

increase in the amount of agent needed. A further problem encountered with more frequent use of some therapeutic agents is the build up of chemical residue within livestock, making the meat worth less and, in some cases, not fit for human consumption. Animals also suffer an increase in handling stress due to the need for increased handling to administer the agents more frequently.

It is also known in the art that handling stress is a contributory factor in livestock weight loss. This, in turn means that livestock use more pasture for less of an economic return. This problem has been found to be particularly acute in animals which have a propensity to be easily stressed.

Clearly, many of these disadvantages could be addressed if animal stress levels could be reduced and the efficacy of therapeutic agents administered could be increased.

US 4,046,890 discloses a pharmacologically active group of benzodiazepine derivatives said to exhibit anthelmintic, anticonvulsant, sedative, and muscle relaxant activity. There is no suggestion that this multiplicity of properties is particularly advantageous, that anthelmintic effectiveness is superior to that of other anthelmintics, nor any suggestion that production gains were achieved using these compounds.

Nutritional supplements have been proposed for use in reducing the effects of stress on animals. Examples of such supplements are described in US 5,505,968 and US 4,600,586. US 5,505,968 discloses a supplement comprising a combination of tryptophan, electrolytes, and amino acids. By improving animal nutrition the effects of stress on meat quality degradation, and loss in liveweight are said to be reduced. The composition does not treat stress *per se*. There is no suggestion to use the composition with therapeutics such as anthelmintics, nor a suggestion that production gains can be achieved with these supplements.

US 4,600,586 similarly discloses a method for producing a feed supplement comprising primarily polyethylene glycol and molasses for use in reducing "lot adaptation stress". Minor ingredients are mixed to homogenicity with an effective amount of polyethylene glycol, then added to molasses and remaining polyethylene glycol. It is stated that if not mixed this way, that is, if merely admixed, then the composition is not effective to treat adaptation stress. Reduction in stress is achieved through increased metabolic utilisation of nutrients. The use of anxiolytics *per se* is not taught, the compositions are not suggested as being generically useful to treat stress. There is no suggestion that broad based production gains can be achieved using the nutritional supplement. There

is no discussion of the combination of the supplement with anthelmintics or other therapeutic agents.

The applicants have now surprisingly found that antistress agents, and combinations thereof, when administered to an animal can generate a broad range of production gains in that animal. This property of antistress agents has not previously been recognised. Moreover, the applicants have also found that selected antistress agents, and combinations thereof, when administered to an animal can generate a broad range of production gains in that animal beyond what might be anticipated from reduction in stress alone.

Moreover, the applicants have also unexpectedly found that selected antistress agents when combined with therapeutic agents can increase the efficacy of the therapeutic agent in a synergistic manner.

An object of the present invention is to provide methods and agents for promoting production gains in animals or at least provide the public with a useful choice.

Other objects will be apparent from the statements and disclosure which follows.

SUMMARY OF THE INVENTION

A first aspect of the present invention provides a method for promoting production gain, in an animal, the method comprising administering at least one therapeutic agent to the animal and reducing the stress experienced by the animal.

In one embodiment, stress experienced by the animal is achieved by reducing physical causes of stress.

In an alternative embodiment, reduction in stress is achieved by administering an antistress agent to the animal.

Animal production gain is preferably a weight gain.

In accordance with a further aspect, the present invention provides a method for enhancing the efficacy of a therapeutic agent, the method comprising the co-administration of at least one therapeutic agent and at least one antistress agent.

In a further aspect, the present invention provides a therapeutic composition comprising at least one therapeutic agent and at least one antistress agent.

In one embodiment, the therapeutic composition is formulated as a slow-release composition.

Preferably, the therapeutic composition is an anthelmintic composition.

The invention extends to the use of antistress agents as adjuvants for therapeutic agents and compositions.

A further aspect of the present invention contemplated is the use of antistress agents as promoters of production gain in animals.

In a further aspect the invention provides a method of promoting production gain in an animal, the method comprising administering to said animal at least one antistress agent.

Desirably, the method comprises administering a composition of the invention.

In a preferred method of treatment, the animal is an animal infected with helminths and the therapeutic composition is an anthelmintic composition.

The invention also provides a second therapeutic composition comprising a therapeutic agent and a nitric oxide promoter.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a bar graph with a superimposed line graph depicting the level of faecal egg estimates on the bar graph and animal growth on the line graph for chronically stressed animals and a control group.

Figure 2 is a line graph depicting the level of faecal egg estimates on the first Y axis and animal growth on the second Y axis line graph for acutely stressed animals and a control group.

Figure 3 is a bar graph with a superimposed line graph depicting the level of faecal egg

estimates on the bar graph and animal growth on the line graph for chronically stressed animals treated with metyrapone.

Figure 4 is a line graph showing the effects of administration of metyrapone on acutely and chronically stressed animals.

Figure 5 is a bar graph showing the effect on animal growth of metyrapone.

Figure 6(a) is a bar graph which shows the differences in average weight of broiler chickens (+/-SED) relative to control birds in treatment groups exposed to cold stress (28°C temperature during weeks 1 and 2). All groups were removed to 21°C after 2 weeks. Symbols above columns represent significant differences in weight ($^{\circ}P<0.05$; $^{+}P<0.01$; $^{*}P0.001$) from control birds.

Figure 6(b) is a bar graph which shows the differences in average weight of broiler chickens (+/-SED) relative to control birds in treatment groups maintained at optimum temperature (32°C) for weeks 1 and 2. All groups were removed to 21°C after 2 weeks. Symbols above columns represent significant differences in weight ($^{\circ}P<0.05$; $^{+}P<0.01$; $^{*}P0.001$) from control birds.

Figure 7 is a bar graph which shows percentage differences in average weight of broiler chickens relative to control birds in treatment groups exposed to cold stress (28°C) during weeks 1 and 2.

Figure 8 is a bar graph which shows average Feed Conversion Ratio (FCR) of broiler chickens from treatment groups exposed to cold stress (28°C) during weeks 1 and 2. Symbols above columns represent significant differences in weight ($^{\circ}P<0.05$;$^{+}P<0.01$) from control birds.

Figure 9 is a bar graph which shows the differences in average Feed Conversion Ratio (FCR) of broiler chickens (+/-SED) relative to control birds in treatment groups exposed to cold stress (28°C) during weeks 1 and 2. Symbols above columns represent significant differences in weight ($^{\circ}P<0.05$;$^{+}P<0.01$) from control birds.

Figure 10 is a bar graph which shows percentage differences in average weight of pigs relative to low stress control animals and adjusted for initial liveweight, breed and sex, maintained under high and low stress conditions and orally dosed with either three concentrations of anti-stress compound or sugar carrier alone. Bar represents 6 week

period when animals were dosed.

Figure 11 is a bar graph which shows gain in weight for the first two weeks after weaning in control animals or animals treated with the experimental compound at the highest doses (Formulation A). Mean and standard deviation presented.

Figure 12 is a line graph which illustrates species dose response differences to multiple dosing with metyrapone mixtures over time. Gain in efficiency calculates the gain in growth alone against increased costs due to increased feed, the metyrapone and potential increased labour costs for administration compared to non-metyrapone control counterparts. This is expressed as a % gain over these control animals. Mean and standard deviation (sd) presented.

Figure 13 is a line graph which illustrates the synergistic effect of vitamin C, isoleucine, leucine and valine on the effects of metyrapone in sheep. Also shows the slight gain from vitamin C, isoleucine, leucine and valine alone without metyrapone.

Figure 14 is a line graph which demonstrates an increased gain by the addition of pyrollopyrimidine (mg) to 0.001 g/kg liveweight metyrapone and 0.1g vitamin C and 0.005g each of leucine, isoleucine and valine. Mean and standard deviation displayed.

Figure 15 is a line graph which illustrates effectiveness of metyrapone alone or in combination in increasing effectiveness of a standard anthelmintic. Mean and standard deviation displayed.

Figure 16 is a line graph which illustrates the average number of lambs live born per ewe and average birth liveweight over 3 seasons for control ewes versus ewes previously treated with metyrapone. Mean and standard deviation presented.

Figure 17 is a line graph which illustrates the average number of lambs live born per ewe and average birthweight over a season with acute treatments. Mean and standard deviation.

Figure 18 is a line graph which illustrates the effects of metyrapone, vitamin C, leucine, isoleucine and valine on liveweight recovery in sheep following surgery under general anaesthesia.

Figure 19 is a line graph which illustrates the effects of metyrapone, vitamin C, leucine,

isoleucine and valine on liveweight recovery in rats following surgery under general anaesthesia.

Figure 20 is a bar graph which illustrates the different stress relieving agents administered to sheep every 2 months with anthelmintics and growth measured over a year. Mean and standard deviation is shown for each treatment group.

Figure 21 is a bar graph which illustrates the effect of treatments on % bodyfat in poultry (mean and standard deviation presented).

Figure 22 is a line graph which illustrates effectiveness of a nitric oxide donor SNAP in increasing effectiveness of a standard anthelmintic. Mean and standard deviation displayed.

DETAILED DESCRIPTION OF THE INVENTION

As discussed above, the applicants have found that antistress agents, when administered to animals have unexpected effects in promoting a broad range of production gains in animals and increasing the efficacy of therapeutic agents. Selected antistress agents exhibit particularly surprising properties in promoting production gain and in increasing the efficacy of therapeutic agents. In an extension of this finding, the applicants have found that production gains may be surprisingly promoted by administering one or more therapeutic agents to an animal and reducing stress experienced by same.

In a first aspect, the present invention provides a method for promoting production gain, the method comprising administering at least one therapeutic agent to an animal and reducing stress experienced by the animal.

The term "production gain" as used herein is a broad term encompassing growth rates, increases in body weight, reproductive success, increase in birthweights, production against or recovery from trauma, efficiency of feed conversion, lean tissue mass, and body fat reduction, or combinations thereof. These terms can be read alone or in combination in place of the term "production gain".

The term "reproductive success" as used herein refers to either or both of the number of animals achieving pregnancy, and the number of live births.

The phrase "protection against or recovery from trauma" as used herein refers to the ability to protect against, ameliorate the effects of, or aid recovery from trauma.

Animals susceptible to treatment according to the invention include humans and other animals. Other animals may encompass pets and livestock including cats, dogs, birds, pigs, sheep, fish, mink, deer, goats, cattle, horses, ducks, chickens and turkeys, but are not limited thereto. Best results are likely to be achieved with animals which are prone to high levels of stress.

Generally, the animals to be treated are sheep, deer, goats, cattle, chickens and pigs.

The term "therapeutic agent" as used herein refers broadly to agents useful in the treatment or prevention of disease or infestation in an animal or otherwise useful in promoting production gain such as animal growth, and well being. Included in the term are vaccines, antibiotics, anthelmintics, other anti-pathogenic agents, growth promoters, performance enhancers, vitamin, amino acid, and mineral supplements, or combinations of these, but are not limited thereto. The term "therapeutic composition" is to be similarly understood as broadly defined.

The term "performance enhancers" is used in the sense that it is employed in the pig and poultry industry to cover antibiotics and oligosaccharides that are primarily prophylactic or therapeutic against disease.

A very broad range of therapeutic agents are known in the art. Vaccines and antibiotics are described for example in *The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal and Antiviral Drugs*, A. Kucers, S.M. Crowe, M.L. Grayson, J.F. Hoy: 5th Edition Butterworth Heinemann 1997; and *Equine Drugs and Vaccines*, E. Kelton and T. Tobin, Breakthrough Pub. 1995; and *Vaccines for Veterinary Applications*, A.R. Peters (Ed.) 1993 all incorporated herein by reference.

Anthelmintics are one preferred group of therapeutic agents for use in the present invention.

A broad range of anthelmintics suitable for use in the methods herein are also known in the art. A general reference text is Chemotherapy of Parasitic Disease; William Campbell, Plenum Publishing 1986 (incorporated herein by reference).

Suitable classes of anthelmintics which can be used include those active against

cestodes, trematodes, nematodes and acanthocephala. The compounds may be selected from the group comprising simple heterocyclic compounds, benzimidazoles, imidazothiazoles, tetrahydropyrimidines, organophosphates, macrocyclic lactones, arsenicals and anticestodal drugs.

More preferably, suitable anthelmintic compounds are selected from the group comprising piperazine, diethylcarbamazine citrate, thiabendazole, fenbendazole, albendazole, oxfendazole, oxibendazole, febantel, tetramisole (levamisole, levamisole hydrochloride), pyrantel tartrate, pyrantel pamoate, morantel tartrate, dichlorvos, milbemycin oxime, eprinomectin, moxidectin, N-butyl chloride, toluene, hygromycin B, sodium arsenamide sodium, melarsomine, praziquantel, epsiprantel, clorsulon, triclabendazole, diazinon, benzimidazole, salicylamide, isoquinoline and cyromazine amongst others.

Preferred commercially available anthelmintics for use in the invention include Fasinex®, Soforen®, Endex®, Combinex®, Parifal®, Neocidol®, Acutak®, Dimpygal®, Nucidol®, Sarnicida®, Topclip®, Sentinel®, Vetrazin®, Avermectin®, Ivermectin® and Doramectin® but are not limited thereto. Combinations of two, three or more anthelmintics with the same or different anti-pest activity are also contemplated.

It will be appreciated by the reader that the amount of agent, delivery and timing varies in accordance with the compound employed, the animal species, bodyweight, age, type of parasite, degree of infestation and whether the treatment is therapeutic or prophylactic. Accordingly, in most cases dosing, and dosages will be carried out according to manufacturers instructions or as otherwise known in the art. For example, for anthelmintics where nematode counts in sheep exceed 600, dosing is generally recommended.

The therapeutic agents referenced above include drenches, pour-on formulations, injectables, oral dosage forms and slow release formulations, amongst others. It will therefore be appreciated that administration of the therapeutic agent at least orally, parenterally, topically and by injection is contemplated. Single and multiple dosing regimes are contemplated. Multiple dosing regimes may comprise administration of two or more agent doses to different sites on, or by different routes of administration to, an animal at the same time. Oral administration may also be achieved by supplying the agent in animal foodstuffs, or water.

In one embodiment, multiple dosing regimes may comprise administration of two or more doses of agents to different sites on an animal over a period of time covering hours, days, weeks or months.

In a preferred anthelmintic treatment regime, for larger animals, animals are dosed every two to four months by a combination of pour-on, injection and oral treatments.

For smaller animals or birds administration may be as a feed constituent on a daily, weekly, monthly, bimonthly or longer basis.

The applicant has also discovered that a combination of selected vitamins and long branched chain amino acids can exhibit a therapeutic effect. The combination comprises vitamin C with one or more amino acids selected from isoleucine, leucine, and valine, but preferably a combination of all three. The therapeutic effects achieved are an increase in effectiveness of therapeutics such as anthelminthics and increase in production gain such as growth in stressed animals. The combinations have also been shown to increase the effects of antistress agents such as metyrapone. The combinations therefor also exhibit antistress agent properties.

Each of the vitamin C and amino acids may be used in dose ranges of from 0.0001 g/kg to 1 g/kg of animal body weight.

Dosage rates for vitamin C when used in combination with antistress agents is generally between 0.005 to 0.5 g/kg, preferably 0.01 g/kg to 0.1 g/kg, and most preferably 0.1 g/kg.

Dosage rates for the amino acids when similarly used in combination with antistress agents is 0.0001 g/kg, and most preferably 0.001 g/kg to 0.005 g/kg and most preferably 0.005 g/kg.

The vitamin C and optimal amino acids may be administered separately, or together in a single composition. Dosage rates for the constituents when used separately can be readily calculated using protocols presented herein.

The present applicant has also found that the animal's state of stress, both acute and chronic, can contribute to the lasting efficacy of either a pour-on, oral or an injectable agent. Animals that have a high acute level of stress, at the time of application, or alternatively a low to high chronic stress load for some time prior to, or after,

application show a lowered efficiency from the dosage and show a quicker re-infestation.

The stress undergone by the animal may be psychological stress or physical stress. Psychological stresses include restraint, handling and novelty stress. Physical stresses include hunger, thirst, fatigue, injury, trauma, surgery or thermal extreme stress. The stress may be also be chronic or acute.

The stress experienced by the animal may also be characterised as being of short duration or alternatively of long duration. In the case of short duration stress reduction, the stress reduction preferably takes place before the administration of the therapeutic agent, but can be after the administration of the agent. In the case of long duration stress reduction, the stress reduction is preferably of an order of at least the time between any agent administrations to the animal.

In one embodiment, stress reduction can be achieved by reducing physical causes of stress, preferably by way of reduced handling of the animals. This can be achieved by reducing intervention with the normal living patterns of the animal. It may include reducing animal (for example dog) and human interaction with the animals, limiting movements, shortening transport procedures and the like. However, physical stress reduction is not always practical.

Accordingly, in an alternative embodiment, stress reduction is achieved by administering at least one antistress agent to the animal.

The term "antistress agent" as used herein refers to compounds or compositions effective in reducing stress. This may be physiological or psychological stress or a combination thereof. Not included are agents which simply act as nutritional modifiers such as foodstuffs, for example, molasses and propylene glycol, or electrolyte combinations. Accordingly, the antistress agents used herein are not simply nutritional modifiers but are also physiological and/or psychological stress reducers *per se*. Any appropriate antistress compounds or compositions known in the art may be employed. The antistress agent is preferably long-acting, although short acting antistress agents are not excluded. In one embodiment, the antistress agent is formulated as a slow-release composition.

Suitable classes of antistress agents, including glucocorticoid inhibitors, corticotrophin releasing hormone inhibitors, ACTH inhibitors, cholecystokinin inhibitors,

benzodiazepines, gamma amino butyric acid potentiators, anti-glutaminergics and serotonergics amongst others. Preferred classes of antistress agents are pyridyl propanones including metyrapone, antiprogestins including mifepristone (RU 38486), and benzoylamino dipropylamino oxopentanoics including proglumide, and peptides such as astressin, an amino acid peptide. Selection of an antistress agent can be made according to broad criteria such as animal species, age, and types of stress. It is noted that antiprogestins are contradicted for use in pregnant or conceiving animals.

As discussed above, the applicant has also surprisingly found that vitamin C and specific amino acid combinations unexpectedly exhibit both therapeutic and antistress properties. Vitamin C alone and combinations with one or more of the amino acids valine, leucine and isoleucine are therefore also classed as anti-stress agents for the purposes of this invention.

More generally, preferred antistress agents include metyrapone, mifepristone (RU 38486), astressin CRH 9-41, proglumide, diazepam, allopregnanolone, dextromethorphan, zimelidine, vitamin C in combination with valine, leucine and isoleucine, and paroxetine but are not limited thereto. Combinations of two, three or more antistress agents with the same or different activity are also contemplated for use herein. Combinations with vitamin C and one or more of the amino acids valine, leucine and isoleucine are also provided. A preferred combination for nonpregnant and nonconceiving animals includes metyrapone and mifepristone (RU 38486). For pregnant or conceiving animals proglumide or astressin and metyrapone is currently suggested.

Astressin is a strong anxiolytic agent and maybe of particular use in high stress situations such as injury, surgery or other trauma.

A particularly preferred antistress agent for use in the present invention is metyrapone. This compound acts to suppress some of the physiological and psychological stress responsiveness in an animal, including elevation of levels of glycocorticoid hormone cortisol.

Current results suggest that astressin, mifepristone, and vitamin C combinations can add to the production gain effects achieved with metyrapone. Vitamin C combinations increase the effects achieved. For combinations with metyrapone the effects of the other agents and combinations may also be increased once metyrapone is saturated.

Antistress agents may again be administered in a broad effective range. Appropriate dosage rates can be selected by the skilled reader according to known protocols for treating a variety of animals. Variation will occur based on the animal to be dosed, age, body weight and the like as discussed above. Dosages within the range of 0.000001 g/kg to 2 g/kg liveweight of total antistress agent whether a single agent or a combination is used, are feasible. Preferred ranges are 0.0005 to 1 g/kg, 0.001 to 0.1, and most preferably 0.01 to 0.1 g/kg. For metyrapone a preferred dosage range is 0.001 to 0.1 g/kg, preferably 0.01 g/kg liveweight.

Dosages within the range may not be suitable for all animals in given circumstances. Animals in different situations may respond differently. As illustrated in Example 8 higher or lower doses of the antistress agent may be appropriate for pigs under stress.

Stressed animals that received this treatment with antistress agents showed approximately the same efficacy of anthelmintics as non-stressed animals and similar growth rates. This point is illustrated in accompanying Figures 2 to 4.

In a second aspect, the present invention provides a method for enhancing the efficacy of a therapeutic agent, the method comprising the co-administration of at least one therapeutic agent and at least one antistress agent to an animal. The antistress agent is preferably selected from the pyridyl propanone, progestin or peptide group of antistress agents, or is a vitamin C combination. Desirably, the agent is metyrapone.

Co-administration encompasses both concurrent and sequential administration. For sequential administration, it is not critical whether the therapeutic agent or antistress agent is administered first. Sequential administration may occur over a period of minutes, hours, or days. However, concurrent administration is preferred.

For concurrent administration, the therapeutic agent and antistress agent are preferably formulated in the same composition.

Accordingly, further aspect of the present invention relates to a therapeutic composition comprising at least one therapeutic agent and at least one antistress agent. The therapeutic and antistress agent may be selected from any of the therapeutics and antistress agents or combinations thereof referenced above or otherwise known in the art. The compositions are useful for promoting production gains in animals. Selected compositions may additionally exhibit synergistic properties. Foremost among these are compositions including at least one agent selected from vitamin C combinations and

the progestin, peptide or pyridyl propanone group of antistress agents.

In a preferred composition, the therapeutic agent is an anthelmintic. In a particularly preferred composition, the anthelmintic is selected from Ivomec, Endex and levamisole and the antistress agent is metyrapone.

A further preferred composition also includes a non-vitamin C antistress agent and vitamin C, one or more of the amino acids selected from valine, leucine and isoleucine, or a combination thereof as discussed above. The addition of this vitamin and amino acids, or combination further enhances the effect of the antistress agent.

The amounts of therapeutic agent(s) and antistress agent(s) in the composition may vary within a broad range, so long as effectiveness is maintained. Antistress agent(s) will generally be present in individual or combined form between 0.0001 to 99.999% of the composition. Suitable concentrations can be calculated based on the weight/kg of liveweight dosage information given above. For best results across species tested to date, it is suggested that between 0.01 and 0.0001 g/kg be used together with 0.1-0.001 g/kg of vitamin C, and 0.005 g of each of valine, isoleucine and leucine.

As discussed above, the compositions of the invention can be formulated for oral, parenteral and topical administration or for injection.

To produce such formulations, the therapeutic compositions of the invention may further contain pharmaceutically or agriculturally acceptable carriers, diluents, excipients, disintegrators, stabilisers, and binding agents and such other materials as are known in the art and customarily employed in such formulations. The compositions may further comprise preservatives, antioxidants, colourants, feedstuffs, nutrients, vitamins, lubricants, salts, lipid membrane transfer facilitators, other therapeutic agents and nitric oxide promoters discussed later herein. This list is illustrative rather than exhaustive of the components of the composition. Suitable substances are well known in the art, for example in Pitha et al 1986; Amorphous water soluble derivatives of cyclodextrins: nontoxic enhancing excipients. J. Pharm Sci 74 (9) 987.

The applicant also hypothesised that the effectiveness of the composition could be further enhanced through the use of a lipid membrane transfer facilitator, to assist the transfer of the therapeutic and antistress agents across cell membranes. This has proved to be the case. Compositions further including a lipid membrane transfer facilitator are therefore contemplated. Facilitators know in the art include pyrolidones such as N-

methylpyrolidone, and pyrimidines such as pyrollopyrimidine, amongst others. Preferred facilitators are pyrollopyrimidine and U-101033E (Also see Andreous P et al. *J. Neuro Science Res.*, 47: 650-654 and Hall E et al 1995 *Acta NeuroChir* 66: 107-113 incorporated herein by reference). The concentration of the facilitator may be from 0.0000001 to 10% of the antistress agent component, preferably 0.01 to 0.1%

Performance enhancers are a group of therapeutic agents including antibiotics and muccan oligosaccharides. They are of particular importance in the pig and poultry industry. An example of such an enhancer for use is Avilamycin at a concentration of between 0.01 to 0.5 g/kg, preferably 0.2 g/kg.

Bio-Mos (Alltech Inc, Kentucky, USA) is an example of a muccan oligosaccharide. An appropriate range for the oligosaccharides is from 0.01 g/kg to 5 g/kg of liveweight, preferably 1 g/kg.

Solubilisers can be important components for solubility in aqueous solutions, and should be non-toxic. Many suitable solubilisers are known in the art. An example of a preferred solubiliser that may be used is 2-hydroxoypropyl-beta-cyclodextrin from 1 to 45% of the solution.

A typical composition for delivery could consist of 0.001% metyrapone, 0.01 % vitamin C, 0.0005% each valine, isoleucine and leucine, 0.0001% pyrollopyrimidine, 5% glucose, 0.1% sodium benzoate and the remainder up to a 1L or 1 kg total coming from a carrier fluid or feed.

In one preferred embodiment, the composition is formulated as a slow-release composition, such as are known in the art. Slow release of the composition may conveniently be achieved through the use of boluses or time release capsules.

Examples of boluses contemplated by the invention are those as set out, for example in GB 2, 122,086, US 3,535,419 and US 5,720,972, which are incorporated herein by reference.

Using the methods and/or compositions of the invention, the applicants have also found that selected antistress agents especially those from the pyridyl propanone group when combined with therapeutic agents or compositions increase the efficacy of the therapeutic agent beyond what would be expected for the agents acting alone. Efficacy is usefully measured either in terms of increased effectiveness or duration of

effectiveness of therapeutic agent. The route of action may vary. For example, in the case of vaccines, the antistress agent may act to increase the antibody titre and hence effectiveness.

The use of these treatments or compositions can therefore reduce the total number of therapeutic treatments needed in a year for effective results. A particular advantage here is that more time may be provided for residue clearance. Alternatively, if the number of treatments remains the same then a corresponding increase in effectiveness of the therapeutic agents should be seen. This means that the effective amount of the therapeutic agent required is reduced.

A still further benefit is reduction in stress at any stage in an animal's life, including in a pen prior to slaughter, where stress can reduce overall meat yield and quality.

Compositions and methods of the invention employing a therapeutic agent and an antistress agent all exhibit a significant benefit in promoting production gains, especially animal growth (e.g. weight gain), reproductive success and improved lean tissue to fat ratios. Animal growth may comprise growth overall during the course of the animal's life or in a pen prior to slaughter. Animal growth in the context of the present invention is primarily measured in terms of weight gain, although other measures are not excluded.

In the experiments carried out to date, and detailed below, the applicants have also surprisingly found that selected antistress agents discussed above, or combinations thereof, when administered to an animal can promote production gain in an animal beyond what might be anticipated from reduction in stress alone.

Accordingly, in a further aspect the invention provides a method of promoting production gain in an animal, the method comprising administering to said animal at least one antistress agent. The present invention also provides the use of antistress agents as discussed above as production gain promoters. The use may be in the preparation of a composition for use as a production gain promoter in animals. The compositions may range from feedstuffs to any of the therapeutic compositions discussed above. The antistress agents to be administered comprise any of those agents or compositions referenced above. Administration dosage levels and protocols are similarly discussed above.

Conveniently, the antistress agents may be used in animal feedstuffs to achieve the

growth promotion benefits. Examples of suitable feedstuffs include hay, silage, haylage, grain, cereals and chicory or any other animal feedstuff produced naturally or artificially manufactured.

One of the production gains identified above is the protection against or recovery from trauma.

The use of antistress agents as protective or recovery aiding agents before, during or after periods of physiological or physical stress as discussed above is specifically contemplated. The use of antistress agents in conjunction with surgery, injury or trauma may be desirable. Examples of trauma include myocardial infarction and cerebrovascular accidents (strokes and brain haemorrhage) but are not limited thereto. That is, the antistress agent may have protective function, especially an organ protective function in the case of physical or psychological stress. Recovery may be conveniently measured through liveweight loss or gain subsequent to injury, surgery or trauma. Animals treated with antistress agents before surgery generally demonstrated no loss in weight, or positive gains compared with weight losses in animals not so treated.

Methods of treating an animal to prevent or aid recovery from stress, particularly surgery or trauma, comprising administering one or more antistress agents alone, or with one or more other therapeutic agents or compositions is therefore contemplated.

The present invention also extends to the use of antistress agents as adjuvants for therapeutic agents. The use may comprise the concurrent or sequential administration of one or more antistress agents with the therapeutic agent(s). Suitable agents and administration protocols are as discussed above.

The use of the antistress agents may also be in the preparation of a composition for use in animal treatment. Examples of such compositions include drenches, vaccines, anthelmintics and the like as discussed above.

In a still further aspect, the invention provides a method of treating an animal, the method comprising administering a therapeutic composition of the invention to said animal. In a preferred method of treatment, the animal is an animal infected with helminths and the therapeutic composition is an anthelmintic composition. Again, any of the compositions and administration regimes referenced above may be employed in this method of the invention.

The applicant has also discovered that the effectiveness of therapeutic agents, especially anthelmintics can be enhanced through the use of substances which increase nitric oxide levels. The applicants hypothesised that the effectiveness of the antistress agents was in allowing natural (endogenous) nitric oxide to facilitate anthelmintic treatment.

Results from the studies conducted suggest that nitric oxide can reduce gut parasite numbers. It seems very likely that this effect occurs via an inflammatory process briefly making the gut wall inhospitable to infestation. Cortisol, the stress hormone, counteracts the effects of nitric oxide and other inflammatory mechanisms. A second route for the generation of immune response to parasites may involve the liberation of certain long chain amino acids from muscle tissue. This amino acid liberation is a known trigger for immune response, and humans with muscular atrophy or high levels of stress are poor at such mobilisation. Acute or chronic stress in animals may thus suppress both this muscle origin and nitric oxide generated immune response and in doing so reduce their synergistic efficiency in decreasing parasite numbers.

The applicants, while not bound by this hypothesis, have shown that exogenously applied substances that promote nitric oxide levels can on their own facilitate anthelmintic treatment.

Accordingly, in a further aspect the invention provides a second therapeutic composition comprising a therapeutic agent and a nitric oxide promoter.

The therapeutic agents include any of the agents discussed above. The nitric oxide promoter may be selected from groups known in the art including L-arginine, diethylamine nitric oxide complex, sodium nitroprusside and S-nitroso-N-acetylpenicillamine amongst others. Appropriate dosage rates range from 0.00001 g/kg livewight to 0.01 g/kg. A preferred range is from 0.0005 to 0.0005 g/kg, preferably 0.0001 g/kg. The compositions may be formulated and administered as discussed above for the first therapeutic composition.

A method of treating an animal using this second therapeutic composition by administering same also forms part of the invention.

Utility

It will be appreciated from the foregoing discussion that antistress compounds with

their potential to promote a broad range of production gains have clear utility in farming, pet care, zoos and animal based industries generally. Major economic and welfare implications are also apparent.

Reduction in animal stress will allow animals to better cope with their environment. This may increase life expectancy, weight and reproductive ability to name a few factors.

Where growth rates can be increased, the time taken for animals to attain required slaughter weight can be reduced, as can feed costs, the two major overheads in the system. For example, in intensive production systems, the most important economic factor is the efficiency of feed conversion or the feed conversion ratio (FCR). Between 60% and 70% of total overheads in the two systems are feed costs, so any procedure or treatment that would increase the efficiency of feed conversion, and thus increase growth rate, would have a major economic impact.

The results obtained also suggest that animals kept at sub-optimal temperatures and given antistress compounds approach and even surpass the FCR and weight gains observed in control animals. There is potential use in reducing heating costs especially in the poultry industry.

Additionally, the use of antistress compounds with performance enhancers, vitamin C and amino acids or combinations thereof can improve production gains and therefore economic returns to farmers.

Other production gains of importance include the ability to generate more lean and less fatty meat. This meets with consumer demand for more healthful meat products. It also has implications for humans wishing to achieve fat loss and lean tissue gain.

The invention will now be described with reference to the following non-limiting examples.

SHEEP TRIALS

In a first series of experiments, sheep were divided into pairs from initial twins. All the animals were grazed together, on the same paddocks, from pairing through to the end of the trial. They were thus exposed to the same potential parasite load and the same

access to feed and water. The animals were also genetically similar (i.e at least one shared parent). Experiments were begun when the animal was 3 months of age.

Animals had ad libitum access to grazing, water and supplementary feed such that intake was never limited.

EXPERIMENT 1

One half of the pairings were rounded up once a week and run through a race (control group). Any normal farm maintenance that was needed was done at this time, so that the time that animals may have been held was variable from week to week but consistent across the entire group and with the experimental group (see below). Faecal samples were also collected and both total egg and nematode egg counts calculated, and visual inspection for ectoparasites made.

The other half of the pairings (chronic stress group) were exposed to the same handling three times a week (consistent with the single weekly procedure above) and in addition to this were run around a paddock by either a human or dog (alternating) for 10 minutes. In this manner a mild, chronic, handling stress was imposed on these animals. Races and handling facilities were cleaned between animal movements to avoid any risk of parasitic contamination.

Animals were subject to the same anthelmintic treatments consisting of three pour-on (Ivomec pour on, MSD 1 ml per 50kg), three oral (Endex, Novartis - 1ml per 5kg) and three injectable treatments (levamisole. 7.5 mg/kg) per year (every four months).

As can be seen from Figure 1 parasitic load during the course of the year was far greater in the stressed group, and growth rate was less than the control group, and the duration of knockdown of parasitic numbers for the set anthelmintic dosage less.

EXPERIMENT 2

In a similar parallel experiment the control group was identical and the paired group to this control (acute stress) received identical treatment to the control group and in addition an acute stress one day prior to anthelmintic treatment. This consisted of chasing the group three times during the day with a dog for 15 min duration each time. The faecal egg count and ectoparasite assessment was the same in both groups at time of the first experimental anthelmintic treatment. Anthelmintic treatment was

administered at the same dosage as one of the four monthly treatments above and then faecal eggs counts followed for up to 6 months, with no further treatment. At average nematode counts of 600-700 treatment is recommended. It can be seen from figure 2 that the knock down time (time following the treatment in which egg counts were maintained below this acceptable number) was less in the acute stressed group. Again growth rate was less in the stressed group.

For both experiment 1 and 2 each group of animals were then crossed-over in experimental treatments (i.e. each group received the treatment of its counterpart). A similar treatment dependent effect on anthelmintic efficacy emerged.

EXPERIMENT 3

In a similar set of experiments to experiment 1, the animals in the chronic stress group also all received a chemical substance metyrapone (in an oral form at 5mg/kg live weight) at the time of anthelmintic treatment. This substance is known to suppresses some of the physiological stress responsiveness, including elevation of levels of the glucocorticoid hormone cortisol.

Animals that received this treatment showed the same efficacy of anthelmintics as the non-stressed groups and similar growth rates. Figure 3 illustrates this data.

EXPERIMENT 4

The acute versus control groups of experiment 2 were also repeated with the acute group receiving metyrapone as above. Again no differences were seen between the acute and control groups when metyrapone was administered.

EXPERIMENT 5

This was again a repeat of experiment 2 but also included the chronic stress group. One treatment was given including metyrapone to stressed (acute and chronic) animals and the time until nematode counts exceeded recommended number for dosing followed. With metyrapone treatments both chronic and acute stressed animals showed no differences to the control group (Figure 4).

EXPERIMENT 6

In this experiment two groups were set up as per the original control groups in experiment 1 (i.e. no additional stresses) and were treated as per anthelmintics in this experiment (i.e. 4 treatments per year). In addition one of these control groups received metyrapone (5mg/kg) at the time of anthelmintic treatment.

Growth rate over the year was compared. The control group that received no metyrapone showed a net gain of mean 12 kg and standard deviation 3 kg. The metyrapone treated group showed 18 kg mean and standard deviation of 2 kg. The results are shown in Figure 5.

EXPERIMENT 7
Poultry Methodology

Objective

This work aimed to investigate the effectiveness of an antistress containing composition or a stress alleviating composition (conveniently referred to as "SAC"), (2-methyl-1,2-di-3-pyridyl-1-propanone, vitamin C and long chain amino acid mix) versus a calorie adjusted control, in lowering the physiological responses to stress and promoting growth in an intensive production systems (broiler chickens). In addition, the effect of the SAC agent in combination with existing industry feed additives (Performance enhancers: antibiotics and indigestible carbohydrates (oligosaccharides) was investigated in broiler chickens.

432 day-old male broiler chicks were used in the experiment carried out over six weeks in a poultry research unit. Chicks were assigned at random to one of 12 groups:

Group 1 - Control 32°C (n=36)
Group 2 - Control 28°C (n=36)
Group 3 - Experimental Formulation A 32°C (n=36)
Group 4 - Experimental Formulation A 28°C (n=36)
Group 5 - Experimental Formulation B 28°C (n=36)
Group 6 - Experimental Formulation C 28°C (n=36)
Group 7 - Performance Enhancer 32°C (n=36)
Group 8 - Performance Enhancer 28°C (n=36)
Group 9 - Oligosaccharide 32°C (n=36)

Group 10 - Oligosaccharide 28°C (n=36)
Group 11 - Experimental Formulation A + Performance Enhancer 32°C (n=36)
Group 12 - Experimental Formulation A + Oligosaccharide 32 C (n=36)

Once selected, groups of 6 birds were housed per cage in heated brooders (i.e. One treatment group (36 birds) per 6 cages). Each group had access to pelleted feed (NRM New Zealand) in excess of requirements during the trial conforming to standard poultry use Ross broiler specification), and water was freely available. During the manufacturing of the feed the following treatments were included.

SAC Agent (2-methyl-1, 2-di-3-pyridyl-1-propanone, vitamin C, valine, isoleucine and leucine mixture), mixed with a glucose-based polymer carrier (0.01g drug to 1g of carrier) before addition to the feed in the following doses.

Formulation A (per kg feed):
0.01g 2-methyl-1, 2-di-3-pyridyl-1-propanone
0.1g Vitamin C
5mg Valine, isoleucine and leucine

Formulation B (per kg feed):
0.005g 2-methyl-1, 2-di-3-pyridyl-1-propanone
0.05g Vitamin C
0.5mg Valine, isoleucine and leucine

Formulation C (per kg feed):
0.001g 2-methyl-1, 2-di-3-pyridyl-1-propanone
0.01g Vitamin C
0.1mg Valine, isoleucine and leucine

Performance Enhancers:
(Avilamycin (Surmax): Elanco Animal Health, Indianapolis, USA)
Dose: < 0.2g/kg (antibiotic concentration of 0.1(g/ml).

Mannan oligosaccharide - indigestible carbohydrate (Bio-Mos: Alltech, Inc.USA)
Dose: 1g/kg

Daily feed intake was recorded for each group of birds, and all birds were weighed weekly.

Birds were either kept at optimum temperature levels (32°C) or exposed to cold stress (28°C) from day 1 until day 14 of the trial. After 14 days they were removed to larger raised horizontal cages where all groups were maintained at 21°C. The birds remained in these cages for the remainder of the trial after which time they were slaughtered. After slaughter, meat from 6 birds per group was analysed for fat composition.

Results

The SAC increased growth rates in broiler chickens exposed to cold stress.

Significantly ($P<0.001$) heavier birds were recorded in the groups receiving SACs. The effect was apparent after only one week of cold stress, and SAC treatment, and was maintained for a week following stress removal.

Three formulations of the SAC were used in the trial and the patterns of their effect, relative to control birds, were slightly different.

Birds receiving Formulation A were 22.9g (12.9%) heavier than control birds after 1 week of cold stress ($P<0.001$), 53.7g (11.2%) heavier at the end of the cold stress period (week 2; $P<0.001$), and 89.3g (9.5%) heavier after 3 weeks of the trial ($P<0.001$).

Birds receiving Formulation C showed a similar, but less dramatic, pattern of growth both during the period of cold stress - week 1: 16.1g (9%: $P<0.01$); week 2: 36.5g (7.6%: $P<0.001$), and after the stressor was removed (week 3: 68.7g (7.3%: $P<0.001$); week 4: 58.5g (3.6%: $P>0.05$).

Birds receiving Formulation B responded with significantly increased weight gain relative to controls for the first 4 weeks of the trial (week 1: 15.8g (8.9%: $P<0.01$); week 2: 36.9g (7.7%: $P<0.001$); week 3: 77.0g (8.2%: $P<0.001$); week 4: 101.7g (6.3%: $P<0.05$).

In comparison to birds given the SAC, birds receiving performance enhancer antiobiotic or oligosaccharide and exposed to cold stress had a lower rate of growth. This was obvious both during the period of cold stress, and afterwards when the birds were transferred to optimum conditions.

However, birds given oligosaccharide performance enhancer were significantly

($P<0.05$) heavier than control birds during the period of cold stress (week 1: 9.6g (5.3%): week 2: 23.2g (4.8%)). This effect declined rapidly when the stressor was removed, and by the end of the trial birds receiving the oligosaccharide were lighter on average than birds in the control group (2223g vs. 2254g).

The weights of birds receiving the antibiotic performance enhancer were not significantly different ($P>0.05$) to control birds during the period of cold stress (week 1: 3.5g (2.0%): week 2: 6.3g (1.3%)). However, when the stressor was removed, the birds showed a significant ($P<0.01$) increase in weight relative to control birds (week 3: 42.6g (4.5%)), although the effect was not maintained during the remainder of the trial (week 4: 35.2g (2.2%).

The increased growth rate due to SACs was not associated with a corresponding increase in feed intake.

Treatment with a combination of Formulation A of the SAC and performance enhancer or oligosaccharide increased the efficiency with which the feed was utilised for weight gain Feed Conversation Ratio (FCR).

Birds that received a combination of Formulation A of the SAC and antibiotic or oligosaccharide performance enhancer consistently showed more efficiency at feed conversion throughout the trial.

Birds given the SAC in combination with the antibiotic performance enhancer were 0.030 (2.8%) more efficient at feed conversion than control birds after 1 week of the trial and 0.179 (8.6%: $P<0.05$) more efficient after 2 weeks.

Similarly, birds given the SAC in combination with the oligosaccharide performance enhancer were 0.022 (2.1%: $P<0.01$) more efficient than control birds after 1 week of the trial and 0.190 (9.2%: $P<0.05$) more efficient after 2 weeks.

Figures 5 to 8 summarises some of this data.

Conclusions

The trial established that the SAC could increase growth rates in chickens.

This increase in growth rate appeared to be achieved entirely by a reduction in the

physiological stress response, or stimulation of another growth pathway. The intensive production system for chickens utilises raised platforms or cages to raise the animals, minimising the potential for parasitic infection. The most significant difference to control was seen in stressed animals suggesting that at least part of the effect was due to modification (reduction) of stress effects on growth.

The SAC appeared to work by increasing the efficiency by which feed was converted into body weight.

Fat analysis of broiler chicken carcasses indicated that the SAC reduced the amount of fat deposited in response to the cold stress.

The data also suggests that broiler chickens kept at sub-optimal temperatures (cold stressed) and given the SAC approach, and even surpass, the efficiency of feed conversion to weight gain observed in control birds at optimum temperatures (1.078 vs 1.068 after 1 week of cold stress: 1.930 vs 2.071 week 2).

EXPERIMENT 8

This experiment was carried out at a pig research unit over 8 weeks. 54 one month-old pigs (27 entire males and 27 females) were assigned at random to one of 6 sex-balanced treatment groups (either 5M:4F or 4M:5F):

Treatment 1 - Control: low stress (n=9)
Treatment 2 - Control: high stress (n=9)
Treatment 3 - Experimental Formulation A: low stress (n=9)
Treatment 4 - Experimental Formulation A: high stress (n=9)
Treatment 5 - Experimental Formulation B: high stress (n=9)
Treatment 6 - Experimental Formulation C: high stress (n=9)

Groups of 3 animals were housed per pen on weaner flat decks maintained at 28-30°C. Each group had access to a commercial-type grower meal and mineral/vitamin supplement (Tasmix pig grower vitamin/mineral premix: Tasmax Vaccines Ltd, Auckland, New Zealand), in excess of daily requirements from a hopper placed in each pen. Daily feed intakes were recorded for each group of animals and water was freely available.

Two levels of stress were imposed on the animals.

Groups 1 and 3: Low level stress associated with normal daily cleaning and feeding and weekly weighing.

Groups 2, 4, 5, and 6: Additional stress imposed on the animals by mixing each group twice weekly. One animal from each of the three groups comprising each treatment was interchanged immediately after weighing.

All animals were weighed twice weekly, before being orally dosed with either formulations of the anti-stress agent (Groups 3-6) or calorie adjusted vehicle (Groups 1 and 2). The pigs remained in pens on the weaner decks for 8 weeks before being slaughtered.

The SAC (2-methyl-1, 2-di-3-pyridyl-1-propanone, vitamin C, valine, isoleucine and leucine mixture) was mixed with a glucose-based polymer carrier (0.01g drug to 1g of carrier), before being dissolved to give the following doses.

Formulation A (per kg bodyweight):
0.5mg 2-methyl-1, 2-di-3-pyridyl-1-propanone
5mg Vitamin C
5mg Valine, isoleucine and leucine

Formulation B (per kg bodyweight):
0.1mg 2-methyl-1, 2-di-3-pyridyl-1-propanone
1mg Vitamin C
1mg Valine, isoleucine and leucine

Formulation C (per kg bodyweight):
0.05mg 2-methyl-1, 2-di-3-pyridyl-1-propanone
0.5mg Vitamin C
0.5mg Valine, isoleucine and leucine

Faecal samples were collected after weeks 1 and 5 and the gastro-intestinal tract of each animal was retained after slaughter to assess the parasite loads of each animal throughout the trial.

Results

During the initial weaning period, a major stress for pigs, control pigs all exhibited significant weight loss. In contrast pigs on formulations A and C gained weight, while

pigs on formulation B did not. This suggests that the right doses of the compounds may prevent stress related to weaning loss of growth in piglets.

Piglets treated with Formulations A and C continued to show increased weight gains and reached goal weights faster compared to control and animals treated with dose B during the course of the mild stress experiment.

Figures 10 and 11 display this data.

EXPERIMENT 9
Dose Response and Dose Composition Relationships

In four different species (sheep, poultry, pigs and rats) different dosages of the compound metyrapone alone or in combination with vitamin C, isoleucine, leucine, valine were tested for growth promotant effects.

These mixtures were administered by oral routes three times over six weeks and a control group was administered a glucose mix at the same time (calorie equivalent). Animal growth in terms of liveweight gains were measured over periods of time, as was feed consumed.

This data together with that described in the examples above for sheep, pigs and poultry was used to work out a dose relationship response between metyrapone and % gain in production. This % gain includes increased growth for increased feed, metyrapone and approximate increased labour costs.

In all species except pigs an increase in gain was seen with an increase in dose of metyrapone levelling out as expected with a positive dose response curve. In pigs a low and a high dose were effective however a mid-range dose did not produce the same gains. This data is displayed in Figure 12.

In all species the addition of vitamin C, isoleucine, leucine and valine increased the measured growth associated with metyrapone. Metyrapone alone also increased growth, except in animals that were deprived of vitamin C and long chain branched amino acids (data not shown). Vitamin C, isoleucine, leucine and valine had a small growth promotant effect in mildly nutritional deprived animals. It is possible that a certain level of these amino acids and vitamin C are needed for metyrapone to have its maximal effect.

A synergistic growth promotant effect of a mix of vitamin C, isoleucine, leucine and valine is thus suggested. Proportional mixture of these compounds seems important, with the most successful mixture being one of approximately: 0.1 g vitamin C and 0.005g each of valine, isoleucine and leucine to each 0.01g of metyrapone.

Figure 13 demonstrates the increased gain in metyrapone effect from the addition of a range of dosages of vitamin c, isoleucine, leucine and valine. It also demonstrates a small gain from these compounds alone.

Adding a further compound, pyrollopyrimidine to the mixture in a composition range of 0.0000001 to 10% of the metyrapone component further enhanced the effectiveness of the mixture. This is shown for sheep in Figure 14.

Pyrollopyrimidine is known in art as a lipid transfer facilitator and it is hypothesised that addition of this compound increased the amount of effective dose of metyrapone, vitamin C, isoleucine, leucine and valine crossing cell membranes.

EXPERIMENT 10

In a further experiment similar to that described in experiments 3 and 4 the increased anthelmintic effect from vitamin C, isoleucine, valine and leucine alone or in combination with metyrapone, and metyrapone and pyrollopyrimidines was tested. Anthelmintics and these agents were given every four months and faecal count calculated each month in between treatments. Figure 15 demonstrates the results which clearly show that treatment with an anthelmintic and metyrapone is more effective than with the anthelmintic alone. The results were further enhanced by the addition of vitamin C, and the amino acids. Further increase in anthelmintic effect was seen when pyrollopyrimidine was added to the latter combination. By themselves, vitamin C and the amino acids had a small effect in increasing anthelmintic effectiveness.

EXPERIMENT 11
Effects of Compounds on Reproductive Success

Female sheep (20 ewes) chosen from original experiments in experiments 4, 5 and 6 were studied for seasonal reproductive success for up to 3 seasons following the original metyrapone treatments. These animals received no further metyrapone treatments and were kept in a flock with a similar selected group of 20 control age and

weight matched counterparts that had not received metyrapone treatment. Over the 3 seasons a similar number of live born lambs were recorded for these two groups of ewes. However, the birthweight of lambs from the metyrapone treated ewes was slightly greater than seen in the control group. Figure 16 illustrates this data.

In a separate experiment using the different sheep with no previous exposure to treatments, 20 age and bodyweight matched ewes were run as a flock. Ten of these ewes received three treatments of metyrapone and vitamin C, isoleucine, leucine and valine at a dosage of 0.001g metyrapone/0.01g vitamin c, 0.0005 g each of valine, isoleucine and leucine per kg liveweight in an oral form without anthelmintics. These three treatments occurred one month prior to conception, in the first and third trimester of pregnancy. The remaining ten ewes received a similar handling and control administration of a glucose-amino acid mixture.

Ewes treated with the metyrapone-vitamin C, isoleucine, leucine and valine mix recorded better reproductive success in terms of number of ewes that achieved pregnancy, number of live born lambs and birthweight of the lambs. Figure 17 illustrates this result.

EXPERIMENT 12

Effects of Compounds on Recovery from Surgical Stress

It has been hypothesised that stress associated with surgery may produce a slower recovery from the surgery. One potential estimate of recovery is liveweight loss or gain subsequent to surgery.

Ten ewes (liveweights 30-40kg) and 20 rats (liveweights 300-350g) underwent minor surgical procedures under a general anaesthesia.

Five of the ewes and 10 of the rats received a treatment of metyrapone (0.001g per kg) combined with vitamin C (0.01g), and valine, isoleucine, leucine each at a dose of 0.0005g per kg. This was delivered orally 3 hours prior to surgery. The other five ewes and 10 rats received an oral glucose mixture with similar calorific properties at the same time as above prior to surgery.

Following surgery liveweights of each animal were obtained daily for 10 days.

Control treated animals all lost liveweight for the first three to five days following

surgery. None of the metyrapone, vitamin C, valine and isoleucine, leucine treated animals lost weight and many in this group gained weight over the 10 days post surgery. Figures 18 and 19 demonstrates this data.

EXPERIMENT 13

Effectiveness of other stress relieving compounds

In a further experiment 35 age and bodyweight matched sheep (ewes) were treated every 2 months with an anthelmintic as per experiments 3 and 4 and one of the following: mifepristone (RU 38486); proglumide; metyrapone all at 0.001g per kg bodyweight; metyrapone at 0.0005g combined with mifepristone (RU 38486) at 0.0005g per kg bodyweight, metyrapone combined with mifepristone (RU 38486) each at 0.001 g per kg; and each of these plus vitamin C (0.01g), leucine, isoleucine, valine (each at 0.0005g), the vitamin C, isoleucine, valine and leucine mix alone or as a control calorie volume matched glucose solution. A further 7 ewes received either astressin 0.0005g or astressin and metyrapone (astressin at 0.0005g and metyrapone at 0.001g) and the vitamin C and amino acid mixture as above.

Bodyweight was measured monthly and animals were treated equivalently in all other aspects.

Figure 20 illustrates the results obtained. Mifepristone (RU 38486), vitamin C and amino acids, and proglumide all had a small positive effect compared to control animals, metyrapone had a larger effect. Adding mifepristone (RU 38486) to metyrapone increased the positive effect slightly suggesting a synergistic and additive effect. More specifically, a 0.0001g/kg mifepristone (RU 38486) dose alone had no effect compared to control but when added to metyrapone increased significantly the effectiveness of that dose of metyrapone, a synergistic effect. Adding control to metyrapone had no effect. At a higher dose of mifepristone (RU 38486) 0.0005 g/kg a small increase in growth over control treatments was observed. When this dose of mifepristone (RU 38486) was added to metyrapone an approximate additive effect was seen.

Astressin had similar effects but also demonstrated a large variability.

The data is usefully summarised in Table 1 below.

Table 1. Dose related effects of mifepristone (RU 38486) or astressin on metyrapone growth increasing properties.

Kg of Growth in 12 months	
Control	5 ± 3
0.0001g/kg mifepristone	4 ± 4
0.0005g/kg mifepristone	8 ± 2
0.0001g/kg metyrapone	13 ± 3
0.0005g/kg astressin	10 ± 4
0.0001g/kg metyrapone + control	14 ± 3
0.0001g/kg metyrapone + 0.0001g/kg mifepristone	17 ± 4
0.0001 g/kg metyrapone + mifepristone	20 ± 4
0.0001 g/kg metyrapone + 0.0005 g/kg astressin	19 ± 5

EXPERIMENT 14

Effect of compound on lean tissue growth.

Animals in Experiment 7 were euthanised and the lean tissue percentage of their carcasses estimated.

The method used was as follows:
SOXTEC EXTRACTION OF FAT FROM RAW MEAT

(Oven dried method) was carried out according to the methods of Firth, N.L., Ross, D.A. and Thonney, M.L. (1985) Comparison of ether and chloroform for Soxtec extraction of Freeze-Dried animal tissues. Journal of the Association of Analytical Chemists 68(6): 1228-1231.

Association of Official Analytical Chemists 1995. Official Methods of Analysis 16th edition 39.1.05. (All references being incorporated herein by reference)

This method is suitable for all meat samples including those containing high levels of fat (>20%). Comparable results were obtained by the oven dried and freeze dried methods for a range of meat samples.

Principle

Samples vary greatly in fat content. Repeatedly washing the sample with petroleum ether by refluxing in a Soxtec apparatus dissolves the fat. The solubilised fat is then collected in the distillation cup and the increase in the weight of the cup represents the dissolved fat.

Sample Preparation

Approximately (3.5 - 4.0g) of meat tissue is required per sub-sample. Samples were prepared in triplicate.

(1) Sample boats made by folding aluminium foil into boats approximately 10cm x 10cm square, wipe with acetone and labelled with sample number on the outside of the foil. Disposable gloves worn when handling meat samples and boats.

(2) For frozen mincemeat - thawed in a microwave and mixed thoroughly.

For frozen whole meat - approximately 35 - 70g of the frozen meat sample defrosted for 30 sec in the microwave oven. Diced into very small pieces using a knife and mixed thoroughly. Fresh samples prepared by dicing and mixed thoroughly.

(3) 3.5 - 4.0g of the sample accurately weighed into the boat and the weight of the sample used recorded. (W1)

Procedure repeated for the remaining two sub-samples of the triplicate.

(NB. For high fat containing samples it is essential to fold the foil with high sides to avoid the fat leaking out).

(4) After weighing the samples were Oven Dried at 95 for 6 hours, then cooled in a dessicator.

(5) Boiling beads placed into clean labelled aluminium extraction cups and dried

in a 105°C oven for 2 hrs. After drying, the cups were cooled in a dessicator and weighed. Weight of cups recorded. (W2)

Data Handling

% Fat = (Cup wt. after extraction) - (Cup wt. before extraction) x 100
Sample wt.

$$\% \text{ Fat} = \frac{W3 - W2 \times 100}{W1}$$

$$\text{Convert to Dry Matter} = \frac{\% \text{ Fat} \times 100}{\% \text{ DM}}$$

Poultry treated with the experimental compounds showed a greater percentage of lean tissue than control counterparts. Bodyfat was 17 +/- 2 , 12+/- 4, 11+/- 3 and 8 +/- 5 (mean and sd) respectively. Figure 21 illustrates this.

EXPERIMENT 15

Effects of nitric oxide donors on anthelmintic efficacy

In a separate experiment 20 sheep (mixed male and females) received standard anthelmintic treatments similar to experiments 3 and 4, with anthelmintics and treatments given every four months. Treatment in 10 of these animals consisted of the anthelmintic dosing and S-nitroso -N-acetylpenicillamine, a nitric oxide donor at a dose of 0.0001g per kg liveweight in an oral form. The other 10 received the anthelmintic and a glucose control. Anthelmintic successfulness in terms of time from treatment until faecal egg count rose to around 600 as described in experiments 3 and 4 was examined. Animals treated with the nitric oxide donor showed a better effectiveness of anthelmintic than control animals. Figure 22 illustrates this.

It will be appreciated by those persons skilled in the art that the foregoing description is provided by way of example only and that the scope of the invention is not limited thereto.

CLAIMS:

1. A composition comprising at least one therapeutic agent and at least one antistress agent.

2. A composition according to claim 1 wherein the therapeutic agent is selected from the group consisting of vaccines, antibiotics, anthelmintics, anti-pathogenic agents, growth promoters, performance enhancers, vitamin, amino acids, and mineral supplements.

3. A composition according to claim 2 wherein the therapeutic agent is an anthelmintic.

4. A composition according to any one of claims 1 to 3 wherein the antistress agent is selected from glucocorticoid inhibitors, corticotropin reducing hormone inhibitors, ACTH inhibitors, cholecystokinin inhibitors, benzodiazepines, gamma amino butyric acid potentiators, antiglutaminergics, and serotonergics.

5. A composition according to any one of claims 1 to 3 wherein the antistress agent is selected from pyridyl propanones, antiprogestins, benzoylamino dipropylamino oxopentanoics, and amino acid peptides.

6. A composition according to any one of claims 1 to 3 wherein the antistress agent is selected from metyrapone, mifepristone, proglumide, astressin, CRH 9-41, diazepam, allopregnanolone, dextromethorpon, zimelidine, and paroxetine.

7. A composition according to claim 6 wherein the antistress agent is selected from metyrapone, mifepristone, proglumide and astressin.

8. A composition according to claim 6 wherein the antistress agent is metyrapone.

9. A composition according to any one of claims 1 to 8 comprising at least two antistress agents, independently selected from the agents according to any one of claims 4 to 8.

10. A composition according to claim 9 wherein the two agents selected are metyrapone and mifepristone, metyrapone and proglumide, or metyrapone and

astressin.

11. A composition according to any one of claims 1 to 10 which further comprises vitamin C.

12. A composition according to any one of claims 1 to 11 which further comprises one or more amino acids selected from valine, leucine and isoleucine.

13. A composition according to any one of claims 1 to 12 which further comprises valine, leucine and isoleucine.

14. A composition according to any one of claims 1 to 13 wherein the, or each, antistress agent is present in an amount of from 0.0005 to 1 g/kg of liveweight.

15. A composition according to claim 14 wherein the, or each, antistress agent is present in an amount of from 0.001 to 0.1 g/kg.

16. A composition according to claim 15 wherein the, or each, antistress agent is present in an amount of 0.01 g/kg.

17. A composition according to any one of claims 1 to 16 which further comprises a lipid membrane transfer facilitator.

18. A composition according to claim 17 wherein the facilitator is pyrollopyrimidine.

19. A composition as claimed in any one of claims 1 to 18 which further comprises a performance enhancer.

20. A composition according to claim 19 wherein the performance enhancer is an antibiotic.

21. A composition according to claim 19 wherein the performance enhancer is an oligosaccharide.

22. A composition according to any one of claims 1 to 21 which is a slow release composition.

23. A composition according to any one of claims 1 to 22 which further comprises at least one pharmaceutically or veterinarily acceptable diluent, excipient, carrier or solubiliser.

24. A method for promoting production gain in an animal, the method comprising administering to said animal at least one antistress agent.

25. A method according to claim 24 wherein the antistress agent is selected from the agents according to any one of claims 4 to 8.

26. A method for enhancing the efficacy of a therapeutic agent, the method comprising the co-administration of at least one therapeutic agent and at least one antistress agent to an animal.

27. A method according to claim 26 wherein the therapeutic agent is an agent according to any one of claims 4 to 8.

28. A method for promoting production gain in an animal, the method comprising administering at least one therapeutic agent to the animal and reducing the stress experienced by the animal.

29. A method according to claim 28 wherein the reduction stress is achieved by reducing physical stress to the animal.

30. A method according to claim 29 wherein reduction in stress is achieved by administering at least one antistress agent according to any one of claims 4 to 8.

31. A method according to any one of claims 24, 25, 26, 28, or 28 to 30, wherein at least two antistress agents independently selected from the agents according to any one of claims 4 to 8 are administered.

32. A method according to any one of claims 24 to 31 which further comprises administering vitamin C.

33. A method according to any one of claims 24 to 32 which further comprises administering one to three amino acids selected from valine, leucine, and isoleucine.

34. A method according to any one of claims 24 to 33 which further comprises administering a lipid membrane transfer facilitator.

35. A method according to claim 34 wherein the facilitator is pyrollopyrimidine.

36. A method according to any one of claims 24 to 35 wherein the, or each, amino acid is administered in an amount according to any one of claims 14 to 16.

37. A composition comprising a therapeutic agent and a nitric oxide promoter.

38. A composition according to claim 37 wherein the promoter is S-nitroso-N-acetylpenicillamine.

39. A composition according to claim 37 or claim 38 wherein the therapeutic agent is an anthelmintic.

40. Use of an antistress agent as an adjuvant for therapeutic agents or compositions.

41. Use of an antistress agent as a promoter of production gain in an animal.

42. Use of an antistress agent in the production of a composition for use in promoting production gain in an animal.

43. Use according to claim 42 wherein the composition is a vaccine, antibiotic, anthelmintic, anti-pathogenic, growth promoter, performance enhancer, vitamin, amino acid or mineral supplement composition.

44. Use according to any one of claims 40 to 43 wherein the antistress agent is selected from the agent according to any one of claims 4 to 8.

Figure 1

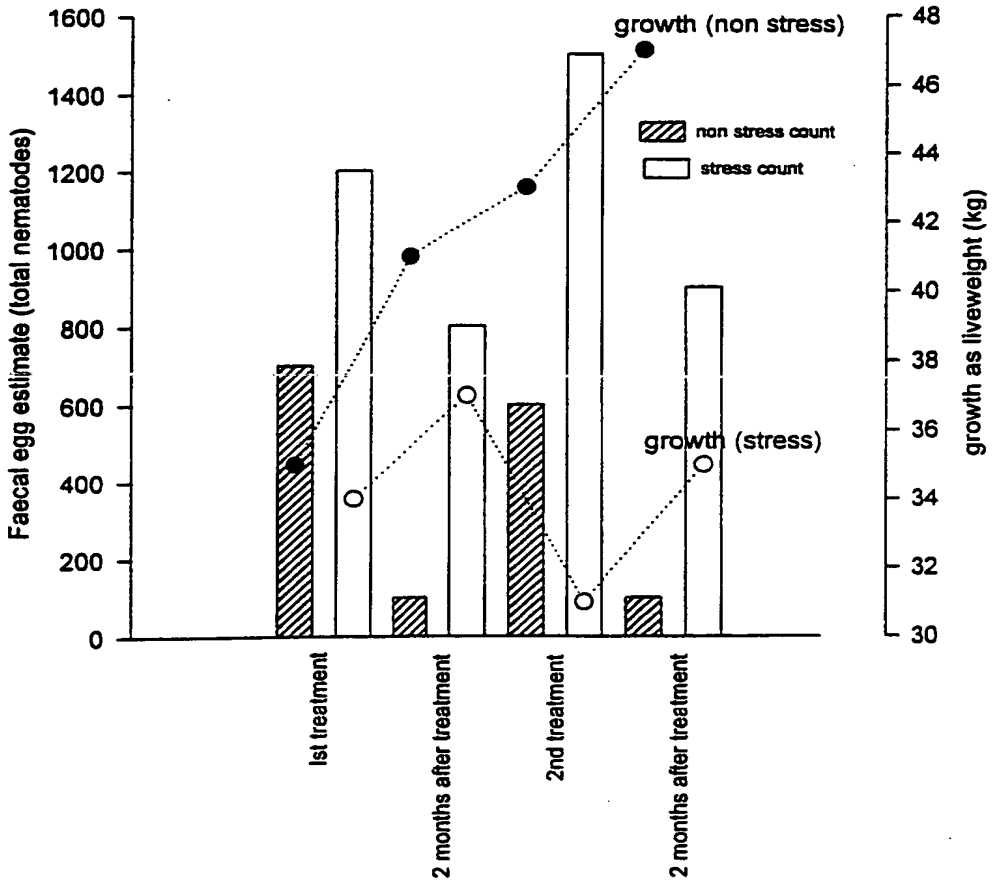

Faecal egg estimate (total nematodes)
1600
1400
1200
1000
800
600
400
200
0
growth (non stress)
non stress count
stress count
growth (stress)
48
46
44
42
40
38
36
34
32
30
growth as liveweight (kg)
1st treatment
2 months after treatment
2nd treatment
2 months after treatment

Figure 2

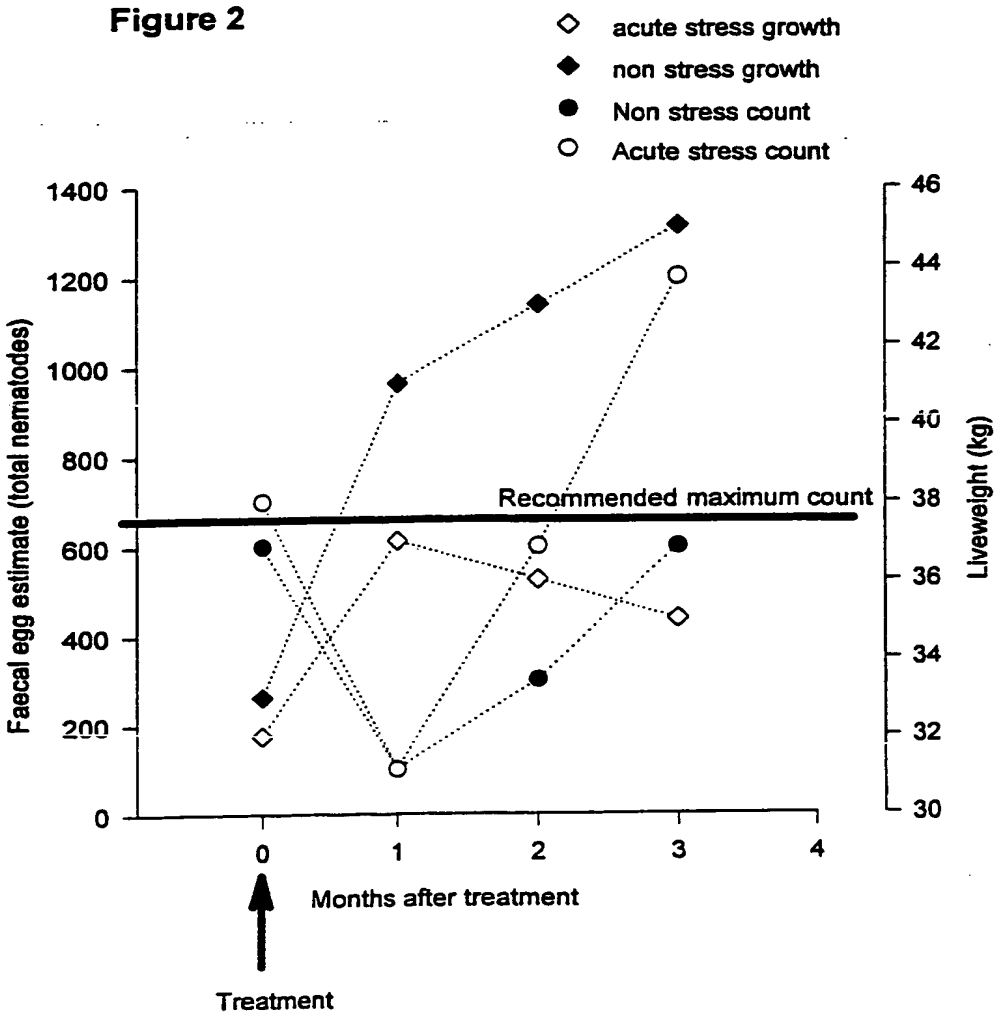

acute stress growth
non stress growth
Non stress count
Acute stress count
Faecal egg estimate (total nematodes)
Liveweight (kg)
Recommended maximum count
Months after treatment
Treatment
0
200
400
600
800
1000
1200
1400
30
32
34
36
38
40
42
44
46
0
1
2
3
4

Figure 3

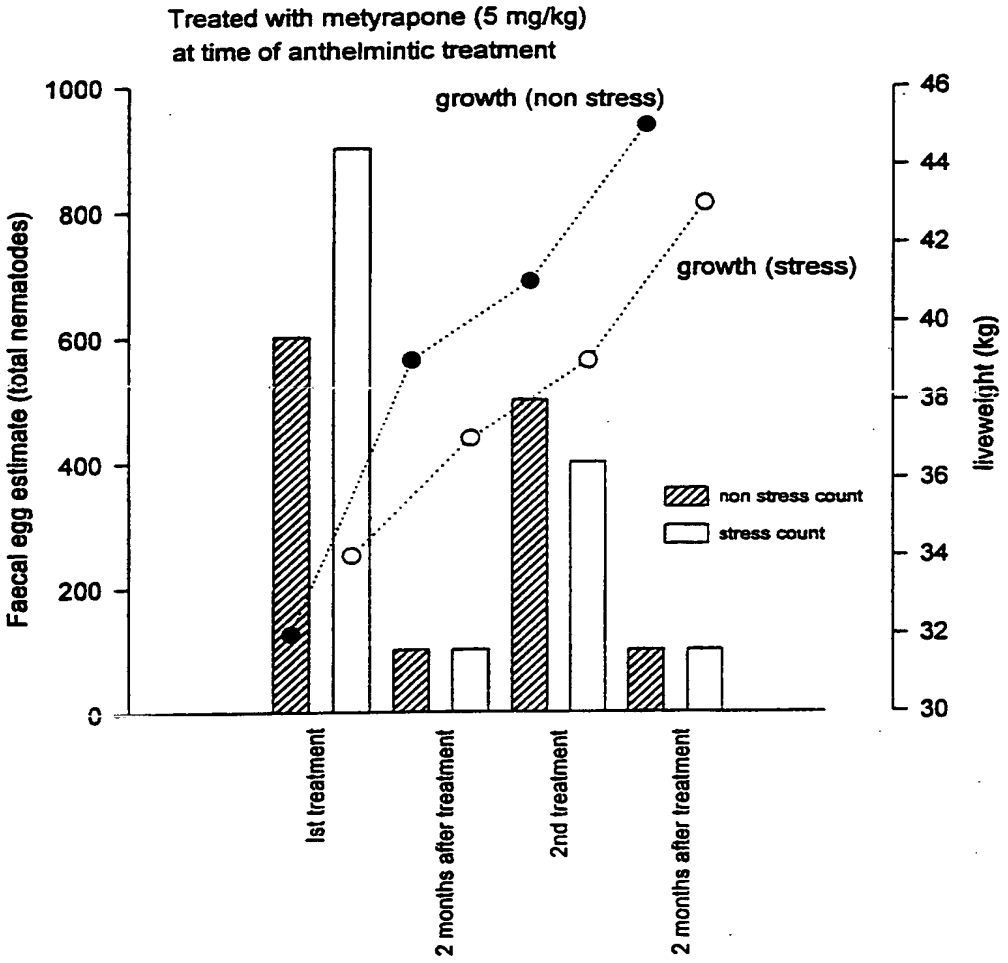

Treated with metyrapone (5 mg/kg)
at time of anthelmintic treatment
growth (non stress)
growth (stress)
non stress count
stress count
Faecal egg estimate (total nematodes)
liveweight (kg)
1000
800
600
400
200
0
46
44
42
40
38
36
34
32
30
1st treatment
2 months after treatment
2nd treatment
2 months after treatment

Figure 4

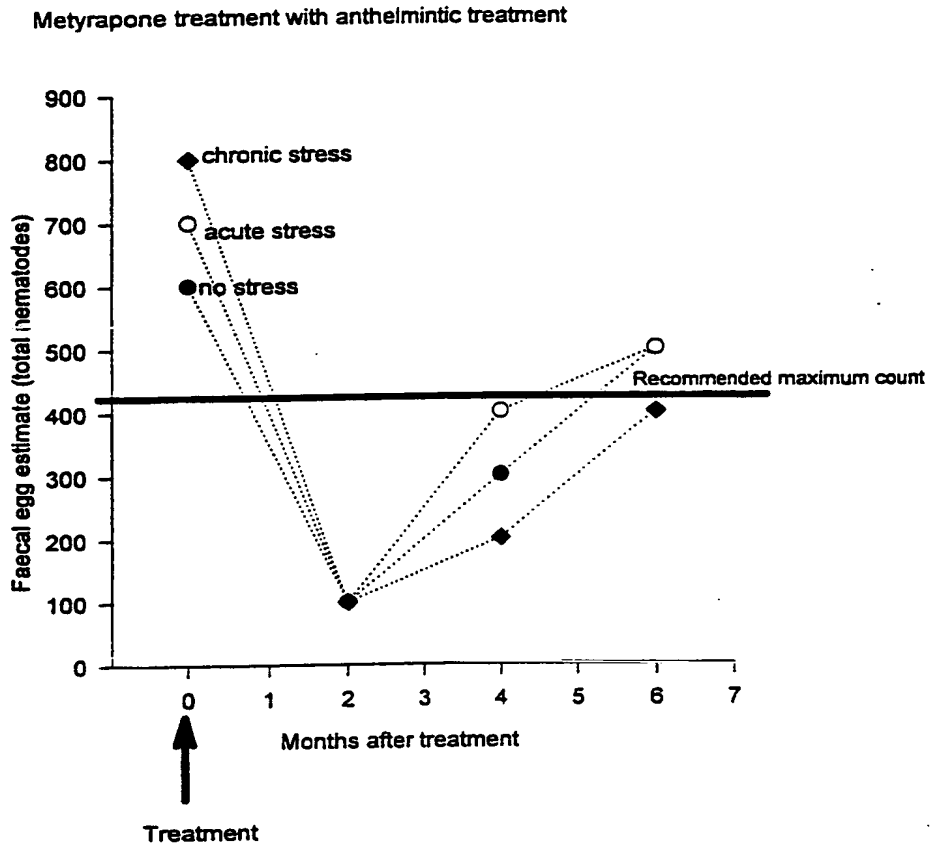
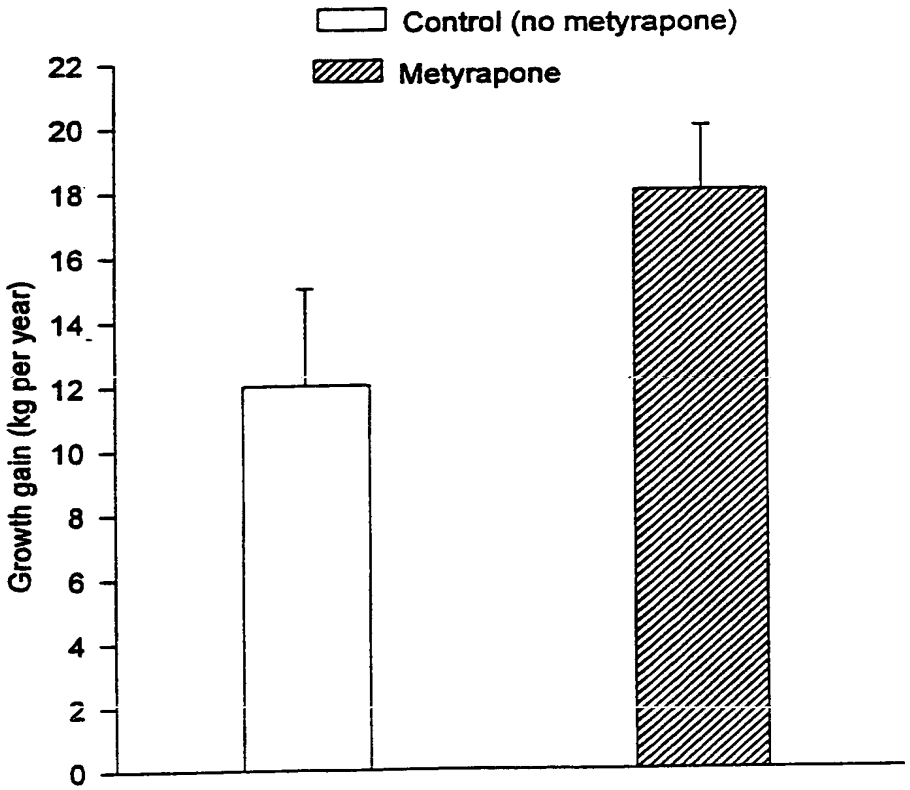

Metyrapone treatment with anthelmintic treatment
Faecal egg estimate (total nematodes)
900
800
700
600
500
400
300
200
100
0
chronic stress
acute stress
no stress
Recommended maximum count
0
1
2
3
4
5
6
7
Months after treatment
Treatment

Figure 5


Control (no metyrapone)
Metyrapone
Growth gain (kg per year)
22
20
18
16
14
12
10
8
6
4
2
0

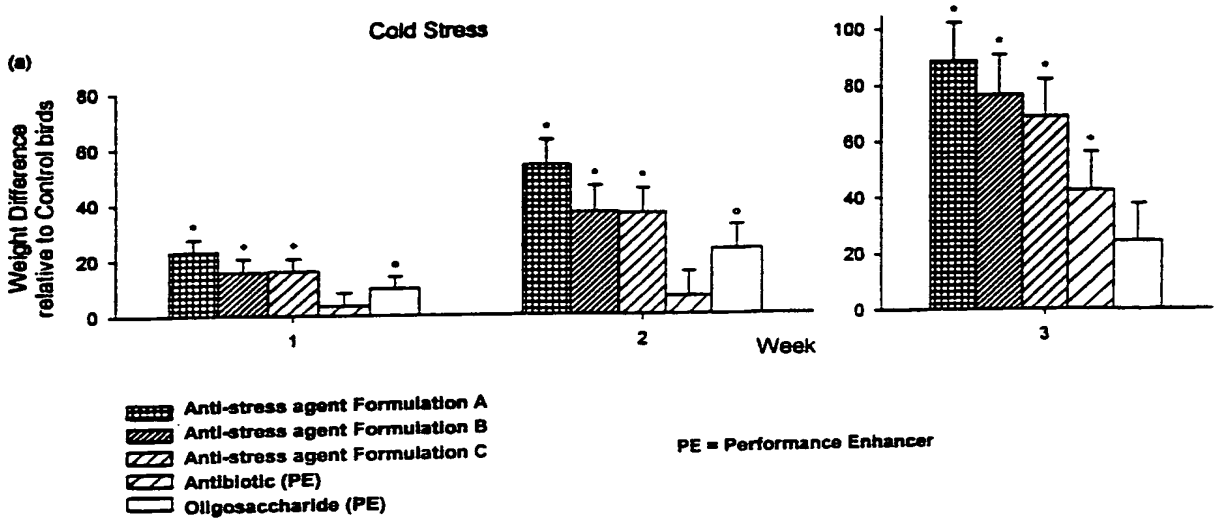


Figure 6(a)

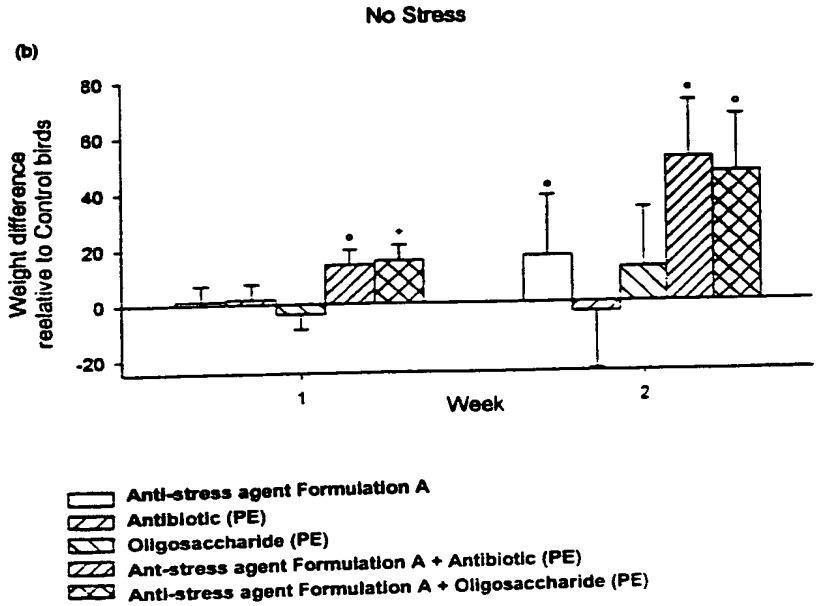


Figure 6(b)

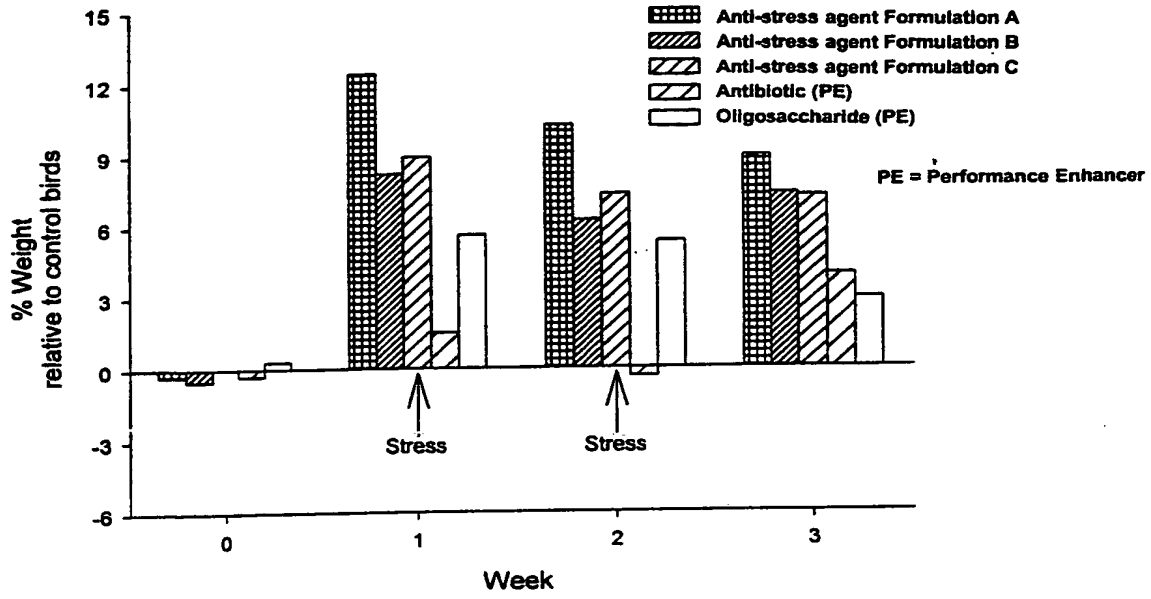


Figure 7

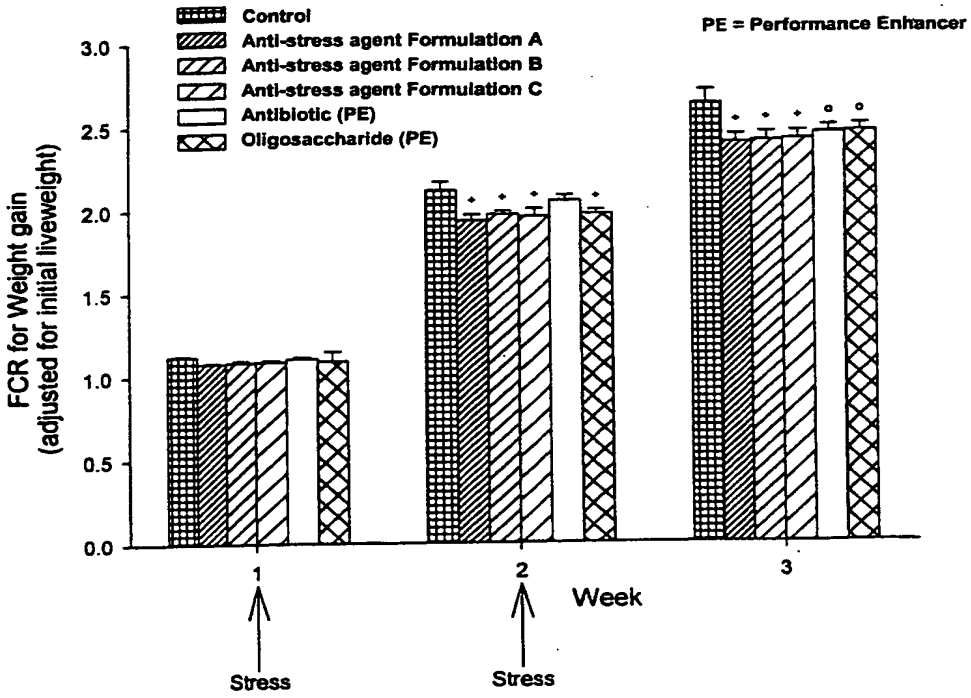


Figure 8

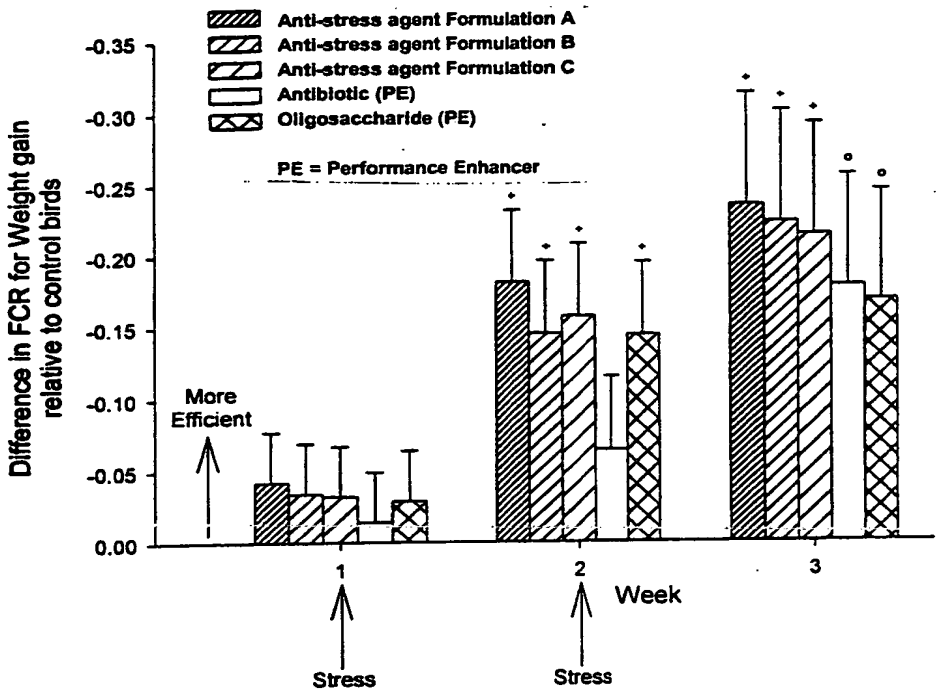
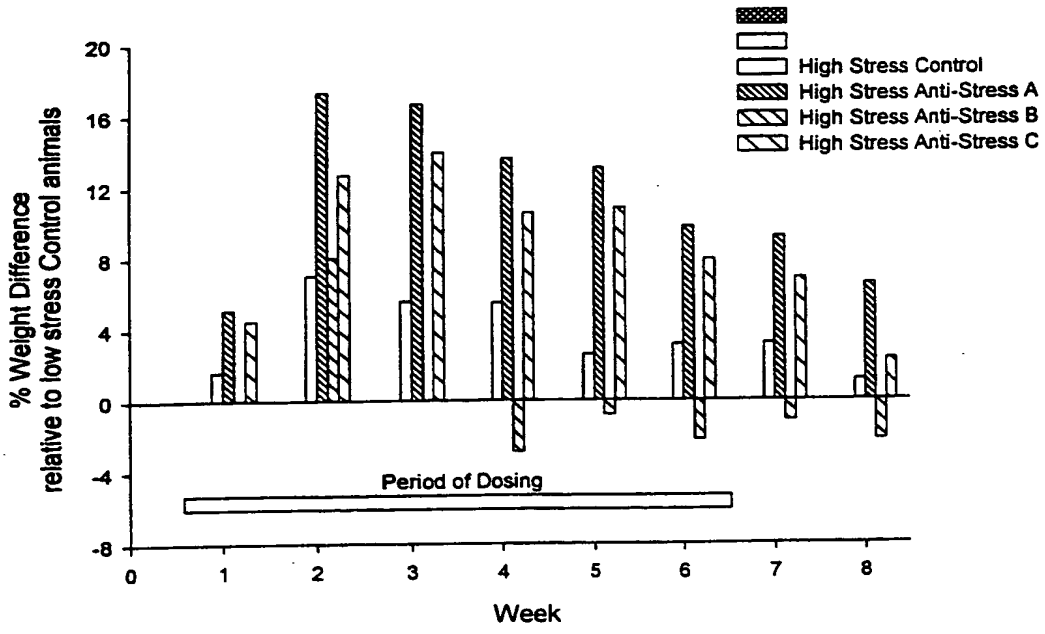


Figure 9



Figur 10

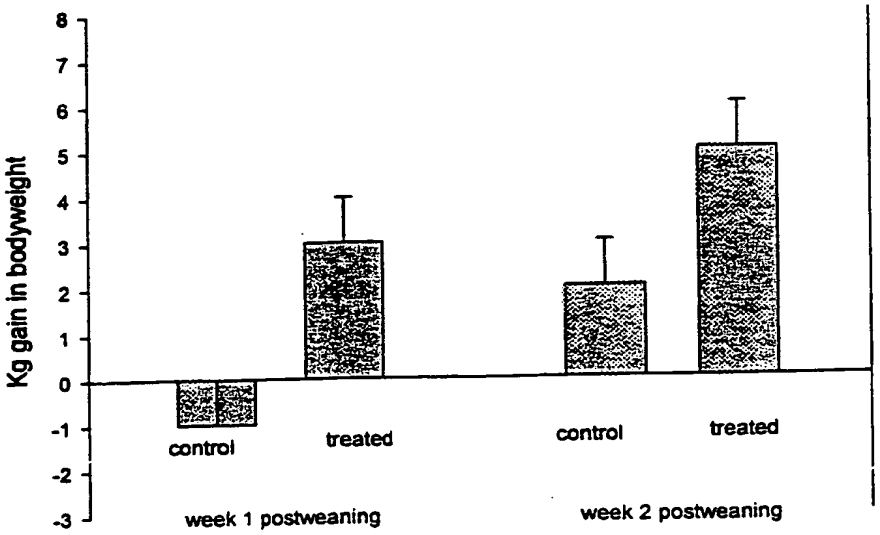
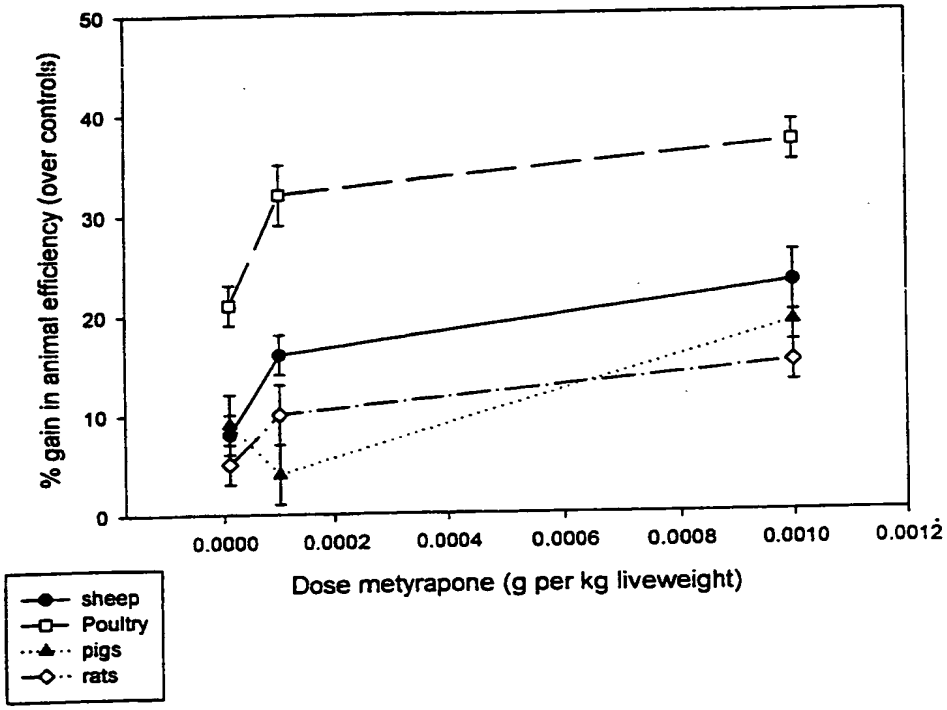


Figure 11



Figur 12

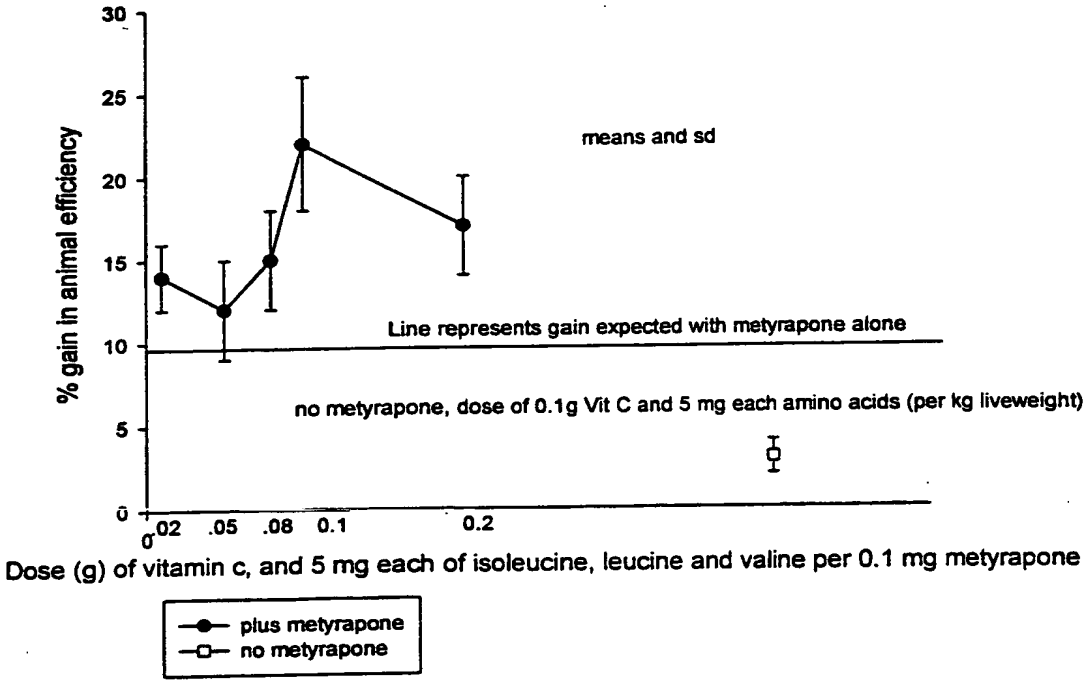


Figure 13

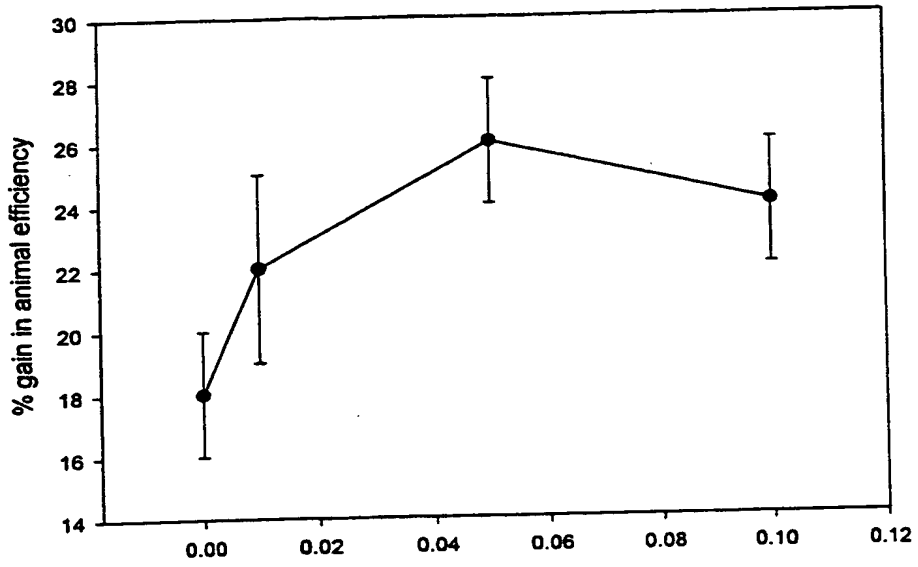


Figure 14

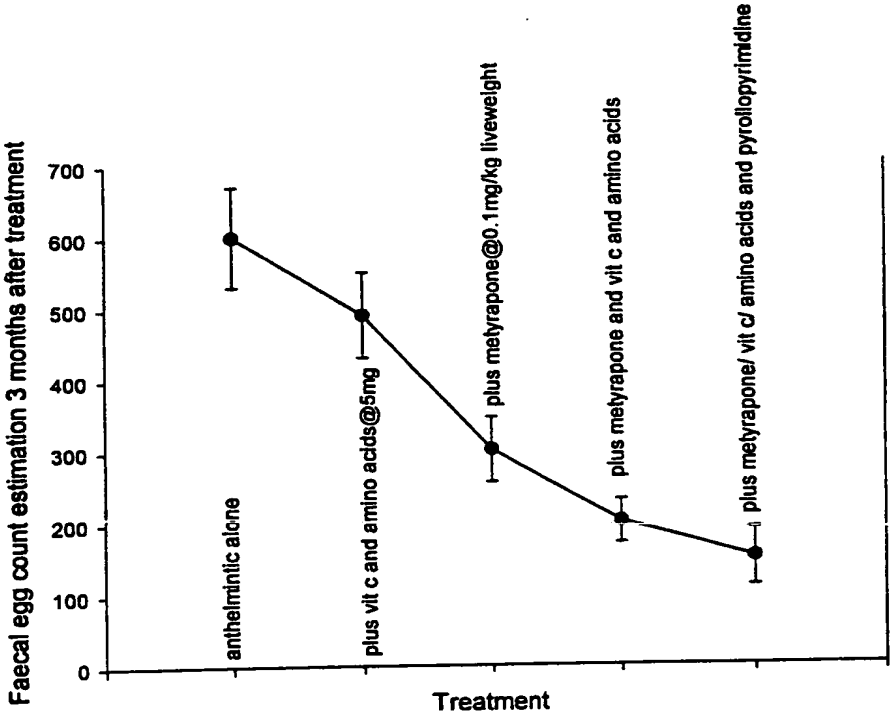


Figure 15

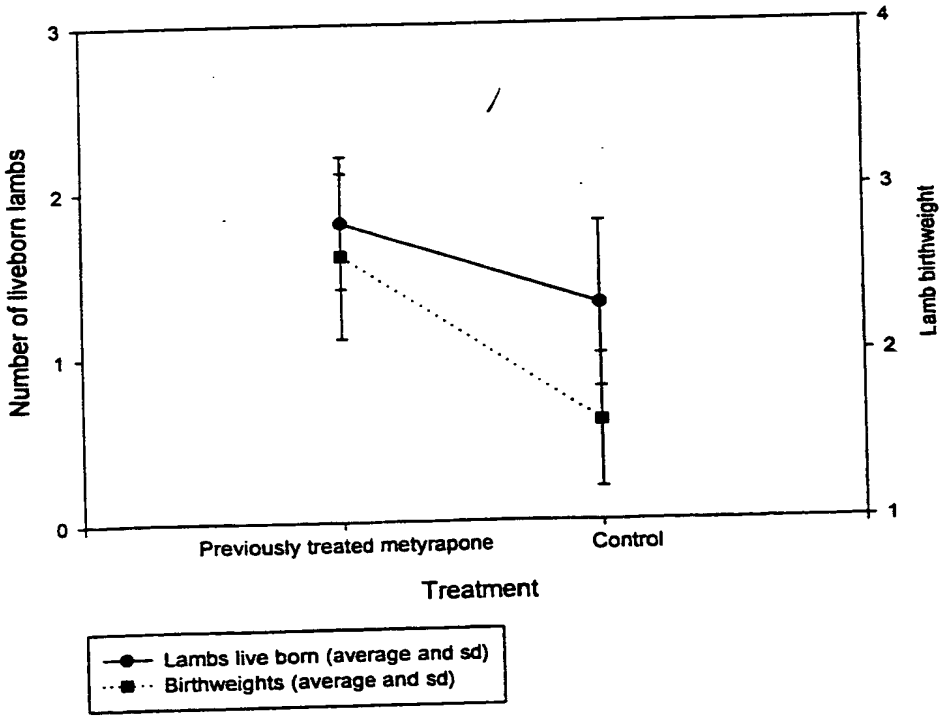


Figure 16

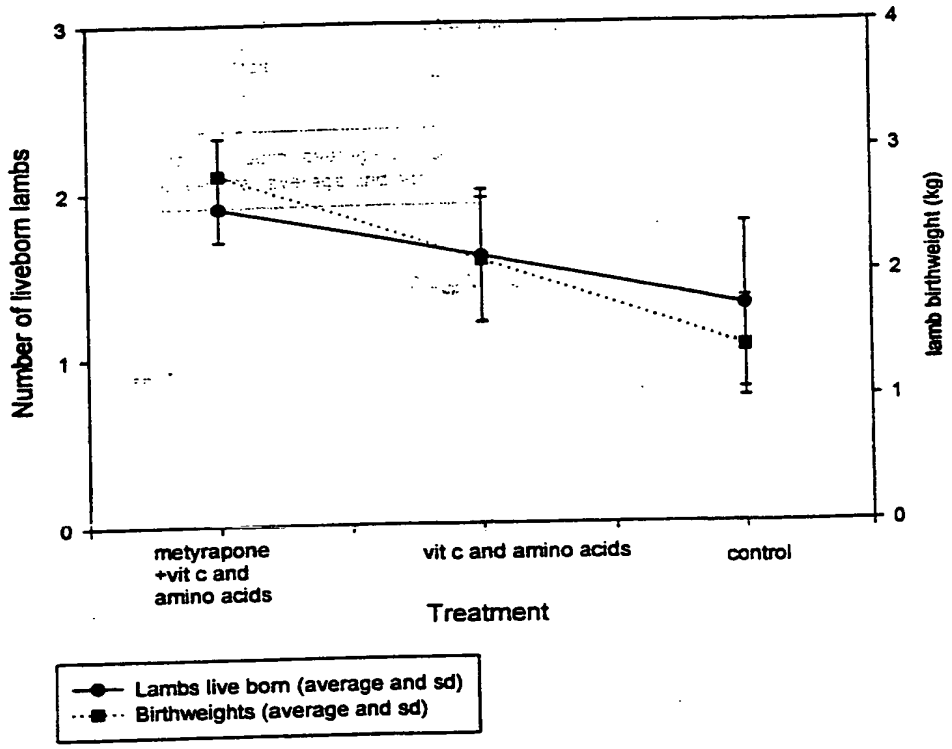
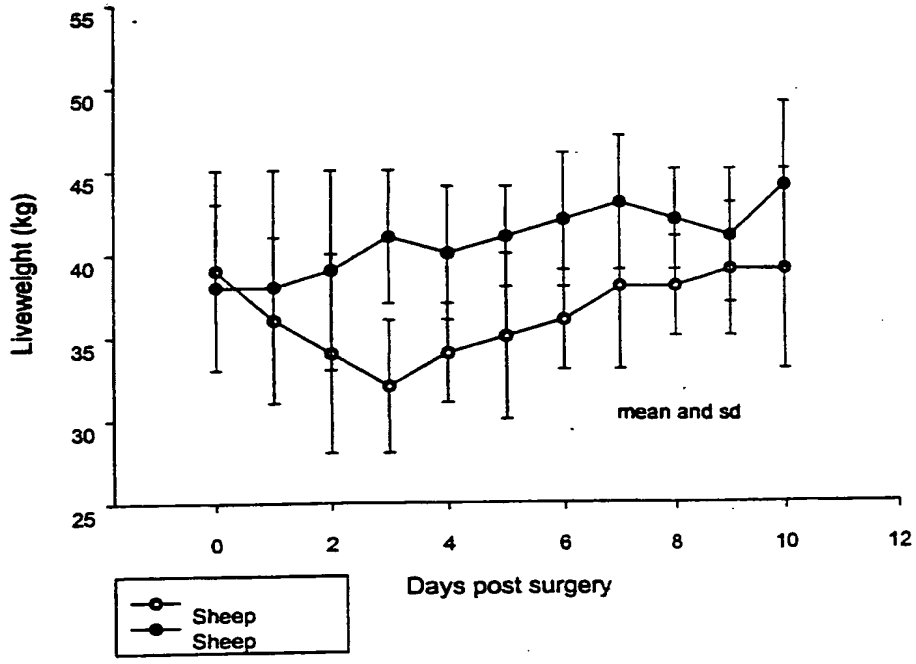


Figure 17



Figur 18

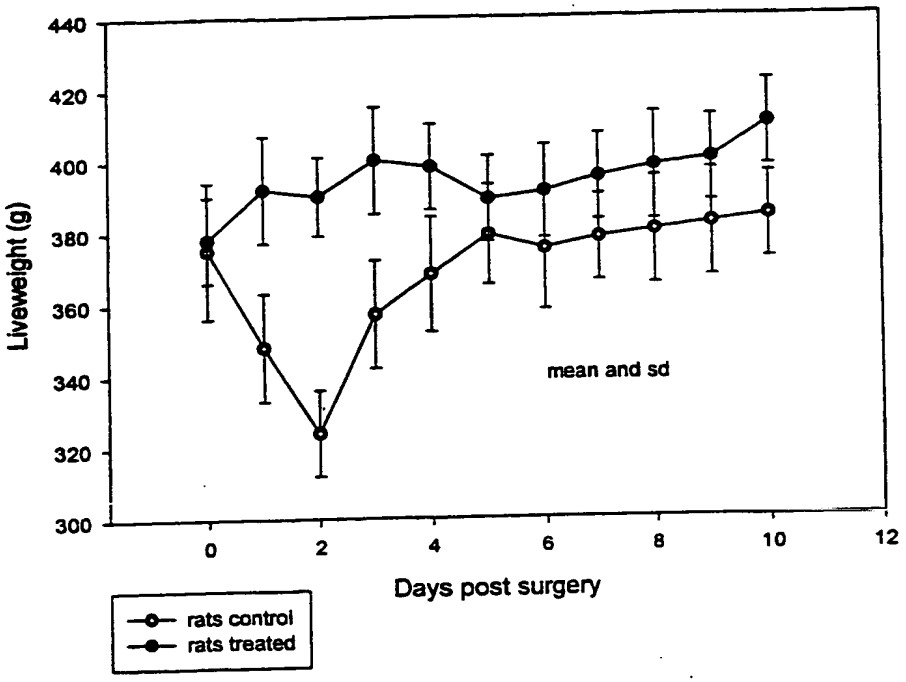


Figure 19

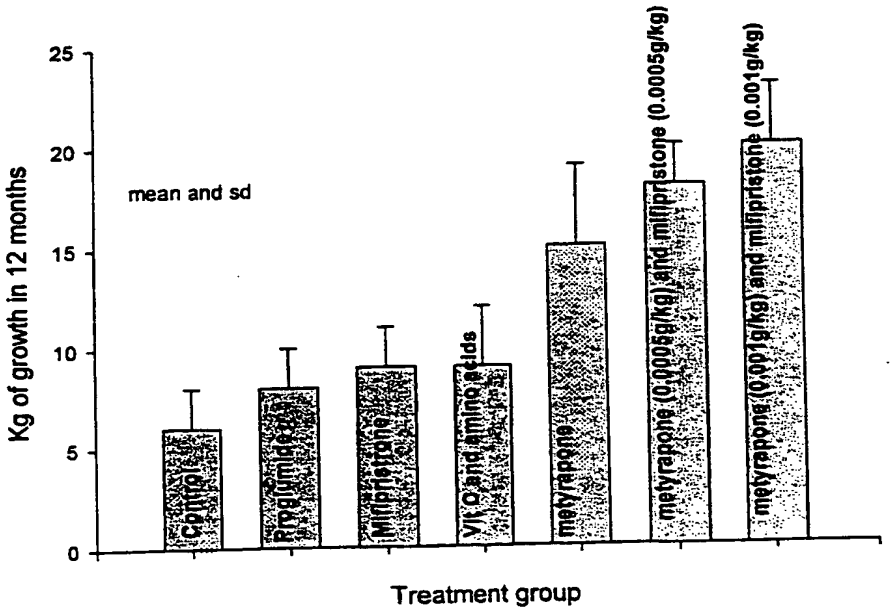


Figure 20

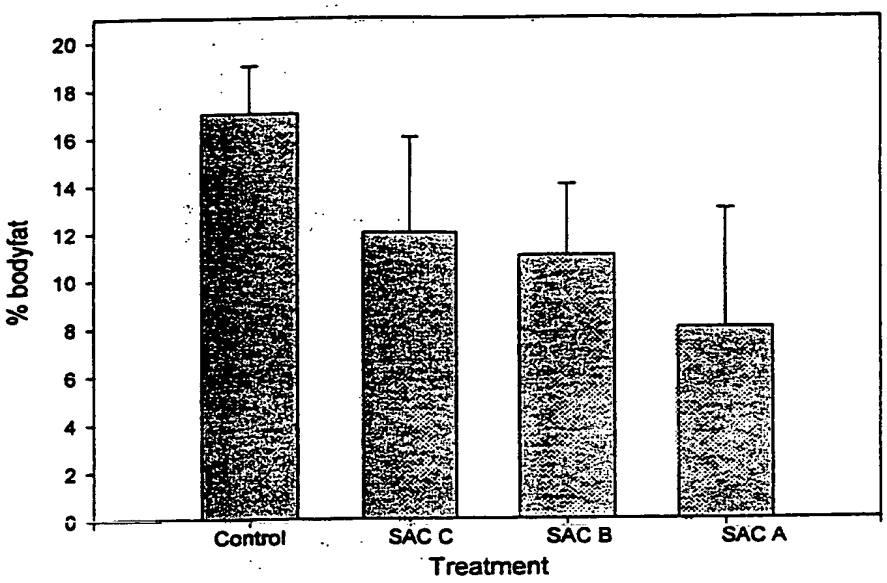
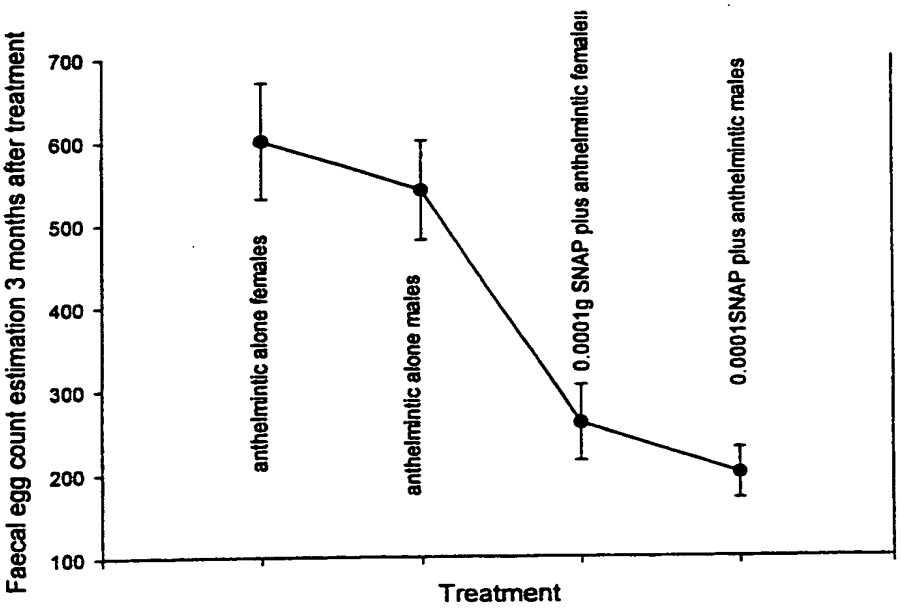


Figure 21



Figur 22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ00/00026

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61K 031/165; A61K 031/44; A61K 031/55; A61K 031/565; A61K 031/57; A61P 025/20; A61P 033/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: A61K, SEARCH TERMS AS BELOW

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC AS ABOVE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT; ESpace; PubMed: (stress OR antistress OR metapyrone OR mifepristone OR progulmide OR astressin) AND (animal OR sheep OR cattle OR bovine OR mammal) AND (weight OR production) AND anthelmintic

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,548,813A (LAWSON, Rommon L.) 22 October 1985 See whole document	1-2, 14-16, 23-24, 26-29, 37, 40-43
P,X	US 5,937,790A (ITU et al.) 17 August 1999 See whole document	1-2, 14-16, 23-24, 26-29, 37, 40-43
X	AU-A-62943/86 (Cetus Corporation) 26 March 1987 See whole document	1-2, 14-16, 23-24, 26-29, 37, 40-43

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
15 June 2000

Date of mailing of the international search report
27 JUN 2000

Name and mailing address of the ISA/AU

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Authorized officer

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ00/00026

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,663,171A (CHEN et al.) 2 September 1997 See whole document	1-2, 14-16, 23-24, 26-29, 37, 40-43
P,X	WO99/52379A (Solutia Inc.) 21 October 1999 See whole document	1-2, 14-16, 23-24, 26-29, 37, 40-43
X	WO95/30418A (The Johns Hopkins University) 16 November 1995 See whole document	1-2, 4, 6-8, 14-16, 23, 37
X	US 5,780,220A (WEINER et al.) 14 July 1998 See whole document	1-2, 4, 6-7, 14-16, 23, 37
X	US 4,576,951A (ROVATI et al.) 18 March 1986 See whole document	1, 6-7, 11, 14-16, 19, 21-23, 37

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ00/00026

Box I **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos :

because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos : **28-29, 37-39**

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The claims as presently drafted are extremely broad and ill defined, and hence were very difficult to search for ISR purposes.

Claim 28 (and its dependent Claim 29) in particular does not appear to define the present invention, in that it is not necessary for an antistress agent to be present - this claim may merely encompass leading the animal patient away from the stressful situation following the administration of a therapeutic agent.

Claim 37 ("a composition comprising a therapeutic agent and a nitric oxide promoter") appears to have merely described the mechanism of action of the antistress agents - they act as nitric oxide promoters in the brain.

As a result of the above, the following inventive concept (as determined by the IS examiner) was searched:

compositions comprising an antistress agent and a therapeutic agent, and the use of such compositions for promoting production/weight gain in an animal.

3. ☐ Claims Nos :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/NZ00/00026

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	4548813	NONE					
US	5937790	EP	848955	JP	10175866		
AU	62943/86	US	4818769	CA	1297003	CN	86106369
		EP	219979	EP	400762	JP	62123129
		US	5102872	US	5100664	US	5503841
		US	5643565	US	5800810	US	6060068
US	5663171	AU	12945/95	CA	2176140	EP	730578
		WO	9514666				
WO	9952379	AU	30122/99	US	6017564		
WO	9530418	AU	24736/95				
US	5780220	AU	25880/95	CA	2190613	EP	759693
		US	5639598	WO	9531901		
US	4576951	DE	3445183	FR	2556216	GB	2151136
		IT	1160131	JP	60197619		

END OF ANNEX

PCT WELTORGANISATION FÜR GEISTIGES EIGENTUM
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INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

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(81) Bestimmungsstaaten: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO Patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Veröffentlicht
Mit internationalem Recherchenbericht.

(54) Title: LICKING STONE

(54) Bezeichnung: LECKSTEIN

(57) Abstract

A licking stone with a solid base material which can be absorbed by mammals when licked, comprising at least one additive to said base material in order to alleviate discomfort. A licking stone of this variety facilitates the administration of medicaments or active substances that alleviate discomfort. The licking stone and the medicament that is to be administered can be arranged in such a way that the animal has constant access thereto. The animal continually receives the medicament or active substance by licking and/or smelling and inhaling as a result of the stone's attractive taste and natural instinct. Since absorption of medicaments is no longer restricted to specific administration of individual doses and feeding times, it is possible to achieve a substantially constant level of action requiring little effort. Constant alleviation of discomfort and a continuous healing process are guaranteed.

(57) Zusammenfassung

Ein Leckstein mit einer festen Grundmasse, die von Säugetieren durch Lecken abtragbar ist, umfasst mindestens einen der Grundmasse zugegebenen Zusatz zum Lindern von Beschwerden. Ein solcher Leckstein erleichtert das Verabreichen von Heilmitteln, bzw. von Wirkstoffen, die Beschwerden lindern. Der Leckstein mit dem zu verabreichenden Heilmittel kann so angeordnet werden, dass das Tier mit Beschwerden immer Zugang hat. Durch einen anziehenden Geschmack und auch durch den natürlichen Beschäftigungsdrang wird gewährleistet, dass das Tier immer wieder durch Lecken und/oder Riechen bzw. Einatmen Heilmittel bzw. Wirkstoff aufnimmt. Weil nun die Heilmittelaufnahme nicht an eine gezielte Verabreichung von Einzeldosen und auch nicht an die Fütterungszeiten gebunden ist, wird mit einem kleinen Aufwand ein im wesentlichen konstanter Wirkstoffpegel erzielt. Dies gewährleistet eine anhaltende Linderung der Beschwerden und ermöglicht einem kontinuierlichen Heilungsprozess.

LEDIGLICH ZUR INFORMATION

Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

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Leckstein

Die Erfindung bezieht sich auf einen Leckstein für Säugetiere.

Bei der Haltung von Säugetieren, insbesondere bei Rindern, Pferden und Sauen ist es äusserst wichtig, dass die Tiere gesund sind. Um die Gefahr von Erkrankungen zu vermindern, werden die Tiere möglichst artgerecht gehalten. Zudem werden Futtermittel eingesetzt, die auf die Ernährungsbedürfnisse der Tiere abgestimmt sind. Ergänzend zum Futter werden etwa Lecksteine eingesetzt. Diese Lecksteine dienen dazu, den Tieren als Ergänzungsstoffe Mineralien, wie Calcium, Phosphor, Magnesium und Natrium, sowie Vitamine und Spurenelemente zuzuführen. Dadurch wird die Gefahr von Mangelerscheinungen und gesundheitlichen Schwächungen vermindert.

Trotzdem erkanken in der Nutztierhaltung immer wieder Tiere. Diese müssen dann entsprechend der jeweiligen Erkrankung mit Medikamenten behandelt werden. Nebst den Kosten für die Medikamente und die ärztliche Verordnung, ist das Verabreichen der Medikamente mit einem grossen Aufwand verbunden. Wenn ein Medikament nicht direkt verabreicht wird, so muss es gezielt dem Futter des kranken Tieres beigemischt werden. Eine erfolgreiche Behandlung ist nur dann gewährleitet, wenn die Beimischung des Medikamentes mit jeder Futtergabe und insbesondere in der richtigen Dosierung erfolgt und das Tier das Futter mit der Zugabe aufnimmt. Inwieweit das Medikament bzw. die benötigte Dosis mit dem Futter aufgenommen wird, hängt von der Konsistenz des Futters, der Konsistenz des Medikamentes bzw. des Wirkstoffes und von der Art der Mischung dieser beiden Komponenten ab. Flüssige Wirkstoffe werden etwa direkt dem Tier zugeführt, oder mit Wasser in einem Kübel dem Tier vorgesetzt, wobei dann aber die Gefahr besteht, dass der Kübel umgestossen und das Medikament verschüttet wird.

Die erfindungsgemässe Aufgabe besteht nun darin, eine Lösung zu finden, die das Versorgen von Tieren mit Heilmitteln bzw. Wirkstoffen mit kleinem Aufwand ermöglicht.

Zur Lösung der Aufgabe wird in Leckstein mit den Merkmalen des Anspruches 1 eingesetzt. Die abhängigen Ansprüche beschreiben bevorzugte Ausführungsformen.

Beim Lösen der Aufgabe wurde erkannt, dass Lecksteine für das Verabreichen von Heilmitteln, bzw. von Wirkstoffen die Beschwerden lindern, eine vorteilhafte Darreichungsform bilden. Ein Leckstein mit dem zu verabreichenden Heilmittel kann so angeordnet werden, dass das Tier mit Beschwerden immer Zugang hat. Durch einen anziehenden Geschmack, der gegebenenfalls durch Ergänzungen aus Karotten, Äpfeln oder Maltose verstärkt wird, und auch durch den natürlichen Beschäftigungsdrang wird gewährleistet, dass das Tier immer wieder durch Lecken und/oder Riechen bzw. Einatmen Heilmittel bzw. Wirkstoff aufnimmt. Weil nun die Heilmittelaufnahme nicht an eine gezielte Verabreichung von Einzeldosen und auch nicht an die Fütterungszeiten gebunden ist, wird ein im wesentlichen konstanter Wirkstoffpegel erzielt. Dies gewährleistet eine anhaltende Linderung der Beschwerden und ermöglicht einen kontinuierlichen Heilungsprozess.

Mit dem Wissen um die vorliegende Erfindung zeigt sich, dass die Lecksteine aufgrund eines Vorurteiles, bzw. aufgrund enger Vorstellungen betreffs deren Verwendungszweck, ausschliesslich aus Ergänzungsstoffen und Trägersubstanz zusammengestellt wurden. Dies ist umso erstaunlicher, als Futter mit Heilmittelzugaben seit langem verwendet werden. Der Grund für das Vorurteil, dass Lecksteine nicht geeignet sind, um Heilmittel abzugeben, geht aus der ursprünglichen Aufgabe des Lecksteines hervor. Der Leckstein wurde entwickelt, um den Tieren auf der Weide Ergänzungsstoffe zuzuführen. Tiere, die zur Milchabgabe in den Stall kommen, können am Futtertrog mit Futter und Ergänzungsstoffen versorgt werden. Die unterschiedliche Bewertung der Abgabe von Futter und des Bereitstellens von Lecksteinen wird vermutlich durch die Tatsache verstärkt, dass Futter so abgegeben wird, dass es vollständig verzehrt wird, der Leckstein wird aber als Depot verstanden, dessen Verzehr nicht überschaubar ist. Wenn Tiere mit Medikamenten behandelt werden, muss das Aufnehmen vorgegebener Dosen gewährleistet sein. Wenn nun der täglichen Futtermenge die Tagesdosis eines benötigten Medikamentes zugmischt ist, kann nach dem Verzehr des Futters davon ausgegangen werden, dass das kranke Tier die benötigte Dosis aufgenommen hat. Dies wird durch den leeren Futtertrog veranschaulicht. Beim Leckstein wird keine kontrollierbare Abgabe erwartet.

Zudem dürfte der Leckstein immer als gemeinsames Depot für eine Gruppe von Tieren betrachtet werden. Dies liegt daran, dass krank Tier nicht auf der gemeinsamen

Weide belassen werden, bzw. dass auf der Weide nur die gesunden Tiere verbleiben. Der Leckstein wird erfahrungsgemäss mit einer Gruppe gesunder Tiere in Verbindung gebracht.

Für die vorliegende Erfindung mussten also mindestens zwei erfinderische Schritte gemacht werden. In einem ersten Schritt musste erkannt werden, dass ein Leckstein nicht nur einer Gruppe von gesunden Tieren, sondern auch einem einzelnen kranken Tier zugeordnet werden kann. In einem zweiten Schritt musste erkannt werden, dass die Stoffaufnahme vom Leckstein steuer- bzw. kontrollierbar ist. Bei Heilmitteln, die nicht in genauen Dosen verabreicht werden müssen, ist die Kontrolle nicht so bedeutsam. Trotzdem musste erkannt werden, dass die Aufnahme vom Leckstein steuerbar ist, weil erst dadurch die Verwendung des Lecksteines als ideale Darreichungsform der verschiedenartigsten Heilmittel einsetzbar ist. Grundsätzlich kann der Verzehr durch die Gewichts- und/oder Volumenabnahme des Lecksteines erfasst werden. Zudem kann aber gerade bei Lecksteinen mit mineralischen Zusätzen davon ausgegangen werden, dass ein Tier automatisch den benötigten täglichen Mineralbedarf abdeckt. Wenn nun dem Lecksteinvolumen bzw. -gewicht das mit dem täglichen Mineralbedarf abgeleckt wird, die Tagesdosis eines Heilmittels zugegeben ist, so ist die Aufnahme der benötigten Heilmitteldosis automatisch gewährleistet.

Das gezielte Anordnen eines Lecksteines im Bereich des Tieres mit Beschwerden ist mit einem wesentlich kleineren Arbeits- und Kontrollaufwand verbunden als das direkte Verabreichen oder das Verabreichen im Futter. Zudem ist eine kontinuierliche Verabreichung und eine Kontrolle der aufgenommenen Menge mit kleinem Aufwand möglich. Die aufgenommene Menge ist beispielsweise an der Abnahme der Lecksteingrösse erkennbar oder durch das oben beschriebene Zumischen im richtigen Verhältnis zum Mineralanteil steuerbar. Es ist auch möglich den Leckstein schichtweise einzufärben, so dass anhand der an der aktuellen Oberfläche sichtbaren Farbe, die bereits abgeleckte Menge ablesbar ist.

Bei natürlichen Heilmitteln sind die Tagesdosen mit grossen Toleranzen verbunden. Dafür kann es sehr wichtig sein, dass die Aufnahme in kurzen Zeitabständen, oder gegebenenfall kontinuierlich erfolgt. Insbes ndere bei ätherischen Ölen zur Behandlung von Atemwegs rkrankungen ist s wichtig, dass das Tier kontinuierlich inhaliert. Dies

wäre bei der Abgabe des ätherischen Öles im Futter nicht möglich. Die Lecksteine sind somit zur Abgabe von Heilmitteln vielseitig einsetzbar. Entsprechend werden anschliessend viele verschiedene Lecksteine mit einem Heilmittelzusatz beschrieben.

Die bekannten Lecksteine werden auf Weiden eingesetzt und müssen somit witterungsbeständig und trotzdem vom Tier ableckbar sein. Die Herstellung von Lecksteinen erfolgt beispielsweise durch das Zusammenstellen einer Trockenmischung, die mittels flüssigen Zutaten und Bindemittel in Breiform gebracht und in eine Form gegossen wird. Durch einen anschliessenden Abbindeprozess wird die gewünschte Härte des Lecksteines erreicht. Eine andere Herstellung sieht vor, dass einer trockenen Pulvermischung aus Mineralien, Vitaminen und Spurenelementen wenig Flüssigkeit zugegeben wird, um diese Mischung anschliessend unter hohem Druck zu einem Leckstein zu pressen. Gegebenenfalls werden aber auch Futterstoffe zu lecksteinartigen Briketts gepresst.

Ein erfindungsgemässer Leckstein umfasst eine Grundmasse mit einer für Lecksteine nötigen Festigkeit und Ableckbarkeit. Als Grundmasse wird vorzugsweise die Masse eines handelsüblichen Lecksteines für die entsprechende Tierart mit Mineralien und/oder Vitaminen und/oder Spurenelementen eingesetzt. Gegebenenfalls umfasst die Grundmasse lediglich Trägerstoffe. Der Grundmasse ist mindestens ein Zusatz zum Lindern von Beschwerden, bzw. ein Heilmittel, zugesetzt. Dieser Zusatz umfasst mindestens einen Wirkstoff der durch Lecken oder gegebenenfalls Inhalieren aufgenommen wird. Der Wirkstoff kann der Wirkstoff eines Naturheilmittels oder auch eines beliebigen Medikamentes sein. Wenn ein homöopathisch wirkendes Mittel eingesetzt wird, so umfasst der Zusatz nicht einen Wirkstoff, sondern ein oder gegebenenfalls mehrere homöopathische Mittel. Diese werden aufgrund der anhaltenden Leckmöglichkeit vorzugsweise in tiefen Potenzen eingesetzt. Es wäre auch möglich Nosoden als Heilmittel einzusetzen. Mit der vorliegenden Erfindung wird somit allgemein eine neue Darreichungsform für Heilmittel zum Behandeln von Säugetieren, wie beispielsweise Pferde, Rinder oder Schweine, offenbart.

Di se neue Darreichungsform ist für alle Heilmitt l geeignet, die über längere Z it bei Raum- bzw. Aussentemperatur haltbar sind. Weil das Tier durch übermässiges Lecken geg benenfalls in kurzer Zeit einen grossen Anteil des Lecksteines aufnehmen kann,

werden vorzugsweise nur Heilmittel eingesetzt, die auch bei den maximal möglichen Aufnahmemengen nicht toxisch bzw. problematisch sind. Es versteht sich von selbst, dass auch Heilmittel die nicht in zu hohen Dosen aufgenommen werden dürfen, eingesetzt werden können, wobei dann beispielsweise die Gesamtmenge im Leckstein unter einer kritischen Dosis liegen wird, oder aber Massnahmen vorgesehen werden, die den Zugang zum Leckstein unterbrechen, wenn dieser in einer vorgegebenen Zeit eine vorgegebene Gewichts-, bzw. Volumenabnahme überschreitet. Die erfindungsgemässe Darreichungsform für Heilmittel ermöglicht den Einsatz von einfachen und insbesondere auch von automatischen Dosiskontrollen.

Weil die Wirkstoffaufnahme durch Lecken am Leckstein aufgrund der festen Leckstein-Grundmasse und der begrenzten Leckfähigkeit nicht über einer oberen ,ermittelbaren Grenze liegen, kann mit der Wahl der richtigen Zusatzmengen eine Überdosierung ausgeschlossen werden. Die langsame bzw. kontrollierbare Abgabe der Wirkstoffe, bzw. Mittel ist ein weiterer Vorteil des erfinderischen Lecksteines

Beim Herstellen eines erfindungsgemässen Lecksteines wird der Zusatz zum Lindern von Beschwerden mit dem mindestens einen Wirkstoff vorzugsweise in die Pulver- bzw. Trockenmischung eingemischt. Anschliessend erfolgen die Schritte zum Verfestigen des Lecksteines mit Flüssigkeits- oder Bindemittelzugabe und anschliessendem Giessen und Abbinden bzw. Pressen, wie sie aus dem Stande der Technik bekannt sind. Bei flüssigen Zusätzen bzw. Wirkstoffen in flüssiger Form ist es gegebenenfalls zweckmässig den Wirkstoff zusammen mit der Flüssigkeits- oder Bindemittelzugabe zuzuführen. Es sind auch Lecksteine in der Form von Briketts mit Heilpflanzen bzw. Extrakten derselben möglich.

Beispiel 1:

Bei Pferden sind Atemwegsbeschwerden bzw. Atemwegsinfektionen häufig mit starken Beschwerden und schleppenden Heilungsverläufen verbunden. Um die Beschwerden, insbesondere etwa den Husten zu lindern, wird nun ein Hustenleckstein mit ätherischen Ölen bereitgestellt. Ein solcher Leckstein wird dem erkrankten Pferd in einem Lecksteinhalter an der Wand der Pferdeboxe oder in der Futterkrippe vorgesetzt. Das Pferd nimmt beim Lecken und Inhalieren ätherische Öle auf. Durch die lösende, bzw.

befreiende Wirkung der Öle werden die Beschwerden gelindert. Es wäre möglich lediglich ein ätherisches Öl einzusetzen. Vorzugswese werden aber Mischungen aus verschiedenen ätherischen Ölen verwendet. Für Atemwegsbeschwerden werden beispielsweise Eucalyptusöl, Pfefferminzöl, Thymianöl, Anisöl und Fichtennadelöl eingesetzt. Es versteht sich von selbst, dass auch andere Öle, insbesondere weitere Kräuteröle und gegebenenfalls auch Pflanzenextrakte eingesetzt werden können. Entsprechend der Art der Atemwegsbeschwerden bzw. der Symtome können verschiedene Lecksteine bereitgestellt werden. Das heisst es könnten spezielle Lecksteine etwa für trockenen Reizhusten, Husten mit Schleim und für Schnupfen mit tropfendem oder zähflüssigem Schleim bereitgestellt werden.

Der Gewichtsanteil der Öle und/oder anderen Mittel kann der Anwendung entsprechend variieren. In einem bevorzugten Standart-Hustenleckstein wird der Gesamtanteil an ätherischem Öl in einem Bereich von 0.1 bis 10 Gew.% liegen. Für spezielle Anwendungen können auch höhere Anteile vorgesehen werden. Eine Standart Ölzusammenstellung umfasst etwa die folgenden Anteile an der gesamten Ölmenge: Eucalyptusöl 25 Gew.%, Pfefferminzöl 50 Gew.%, Thymianöl 10 Gew.%, Anisöl 5 Gew.% und Fichtennadelöl 10 Gew.%. Es versteht sich von selbst, dass einzelne Öle weggelassen und die verschiedenen Anteile um bis zu 20 Gew.% geändert werden können. Das Weglassen einzelner Öle kann die Akzeptanz durch das Tier erhöhen. Es versteht sich von selbst, dass die für Pferde entwickelten Hustenlecksteine auch für Rinder und Schweine einsetzbar sind. Gegebenenfalls werden sie entsprechend den Vorlieben und Bedürfnissen der jeweiligen Tierart angepasst.

Beispiel 2

Zum Lindern von Magen-, Leber- und/oder Gallebeschwerden werden Lecksteine zusammengestellt, die mindestens einen Wirkstoff aus Pfefferminze, Wermut, Kümmel, Fenchel und/oder Tausendgüldenkraut umfassen. Der mindestens eine Wirkstoff kann in der Form von Pflanzenteilen, vorzugsweise in der Form einer Kräutermischung, mit Anteilen der einzelnen Pflanzen von 0.5 bis 10, insbesondere von 1 bis 5 Gew.% des Lecksteingewichtes vorliegen. Eine Mischung di sich bei Versuch n bewährt hat umfasst 4 Gew.% Pfefferminze, 1 Gew.% Wermut, 2 Gew.% Kümmel und 2 Gew.% Fenchel. Es versteht sich von selbst, dass einzelne Kräuter geggelassen oder durch an-

dere ersetzt werden können. Zudem können die angegebenen Anteile auch um bis zu 5 Gew.% höher oder 2 Gew.% tiefer liegen. Anstelle der Zugabe von Pflanzenteilen können die Wirkstoffe auch in der Form von ätherischen Ölen mit einem Öl-Gesamtanteil von 0.1 bis 10 Gew.% des Lecksteines zugegeben werden. Vorzugsweise sind die relativen Verhältnisse zwischen den einzelnen Ölen analog zu den oben angeführten Anteilen der pflanzlichen Zugabe.

Beispiel 3

Die Pansenübersäuerung (Pansenacidose) ist eine Beschwerde, die bei Wiederkäuern auftritt. Um diese Beschwerde zu lindern bzw. zu beseitigen muss der pH Wert verändert werden. Dies erfolgt durch mindestens einen basischen Wirkstoff. Vorzugsweise wird eine Mischung mit grossen Anteilen von Natriumbikarbonat und Magnesiumoxid eingesetzt. Versuche haben gezeigt, dass ein Leckstein hergestellt werden kann, der 60 Gew.% Natriumbikarbonat, 30 Gew.% Magnesiumoxid, 9 Gew.% Salz und 1 Gew.% Aromastoffe umfasst. Diese Zutaten werden gemischt in Breiform gebracht und anschliessend erhärtet oder gepresst. Es versteht sich von selbst, dass auch andere oder weitere basische Zusätze vorgesehen werden können, wobei die Anteile entsprechend angepasst werden. Wenn der Gesamtanteil der basischen Wirkstoffe kleiner ist als der oben angeführte hohe Anteil von 99%, so muss das Tier entsprechend mehr lecken, um die gleiche Linderung zu erzielen.

Beispiel 4

Gegen Blähungen wird ein Leckstein mit mindestens einem blähungslindernden Zusatz eingesetzt. Gegebenenfalls umfasst dieser Zusatz Fenchelöl und/oder Kümmelöl mit Anteilen im Bereich von 1 bis 5, vorzugsweise von im wesentlichen je 2 Gew.%. Ein schaumbrechendes Mittel bzw. ein Tensid ist mit einem Anteil von 1 bis 10 vorzugsweise im wesentlichen von 6 Gew.% zugefügt.

Beispiel 5

Ein weit res Ausführungsbeispiel eines erfindungsgemässen Lecksteines umfasst mindestens inen Zusatz, der Nieren- und/oder Blasenbeschwerden, insbesondere

Harnwegsentzündungen, lindert. Zudem k¨nnen auch Beschwerden von Euterödemen aufgrund mangelnder Ausscheidung behoben werden. Vorzugsweise wird ein Wirkstoff aus Brenessel und/oder Wacholder, insbesondere Wacholderöl und Brenesselextrakt, verwendet. Dabei liegen beide Anteile im Bereich von 1 bis 10 Gew.%, vorzugsweise bei im wesentlichen 5 Gew.%.

Beispiel 6

Leckstеine können auch zum Entwurmen eingesetzt werden. Dazu wird mindestens ein Zusatz vorgesehen, der Parasitenbefall, insbesondere Eingeweide-Wurmbefall, lindert. Vorzugsweise wird Piperazin und/oder mindestens ein Wirkstoff des Farnkrautes in den Leckstein eingebracht, wobei der Anteil des Zusatzes zwischen 2 und 20, vorzugsweise bei im wesentlichen 10 Gew.% liegt.

Beispiel 7

Bei Milchfieber-Beschwerden, insbesondere bei Schweinen wir ein Leckstein vorgeschlagen, der einen Zusatz zum Lindern von Milchfieber-Beschwerden, bzw. Metritis, Mastitis und/oder Agalaktie umfasst. Dieser Zusatz umfasst einen natürlichen oder künstlichen antimikrobiellen Wirkstoff, beispielsweise Zinkbacitracin in einem Anteil von 1 bis 5, vorzugsweise von im wesentlichen 2 Gew.%.

Beispiel 8

Für ein besseres Wohlbefinden und zum Verkleinern der Übertragungsgefahr von Krankheiten wird ein Leckstein mit mindestens einem Zusatz, der Insektenbefall lindernd ist, eingesetzt. Der Befall soll etwa aufgrund einer vom Zusatz ausgehenden Ausdünstung reduziert werden. Als Zusatz wird vorzugsweise Knoblauch in der Form von Knoblauchpulver, mit einem Anteil von 2 bis 15, vorzugsweise von im wesentlichen 10 Gew.% oder Knoblauchöl mit einem Anteil von 0.1 bis 4, vorzugsweise von im wesentlichen 1 Gew.% verwendet.

Beispiel 9

Bei Schweinen führen enge Verhältnisse und Stress zu Kannibalismus. Um dies zu verhindern wird ein Leckstein zur Verfügung gestellt, der mindestens einen stresslindernden Zusatz, vorzugsweise Baldrian umfasst, wobei etwa gemahlene Baldrianwurzeln, vorzugsweise mit einem Anteil von 1 bis 10 Gew.% und/oder Baldriantrockenextrakt mit einem Anteil von 0.5 bis 5, insbesondere von 2 Gew.% zugegeben werden bzw. wird.

Anhand dieser Vielzahl von Ausführungsbeispielen ist die Breite der Erfindung geoffenbart. Die Erfindung ist nicht auf einzelne Beispiele eingeschränkt. Die in den Beispielen aufgeführten Heilmittelzusätze dürfen ohne Zulassung verwendet und rezeptfrei verkauft werden. Wenn nun ein Landwirt oder Pferdehalter für die verschiedenen Beschwerden Lecksteine vorrätig hat, kann er diese jeweils direkt bei den ersten Symtomen einer Erkrankung oder gegebenenfalls auch präventiv einsetzen. Durch die rechtzeitige Verwendung von erprobten Naturheilmitteln kann häufig auf eine ärztliche Untersuchung und auf die Anwendung von rezeptpflichtigen Medikamenten verzichtet werden. Die Lecksteine mit den verschiedenen Heilmittelzugaben können durch Form- und/oder Farbgebung unterscheidbar ausgebildet werden. Sie müssen lediglich beim Liegeplatz des Tieres angeordnet werden. Auf das Lesen von Dosierungsangaben, das Beimischen in Futtergaben und das getrennte Verfüttern dieser Futtergaben kann verzichtet werden. Weil das Lagern und Einsetzen von Lecksteinen mit Heilmitteln sehr einfach ist, kann mit einem effizienten Einsatz bzw. einer hohen Motivation des Tierhalters gerechnet werden.

Wie bereits erwähnt, eignet sich der Leckstein auch als Träger von rezeptpflichtigen Medikamenten. An speziellen Haltern können gegebenenfalls auch äusserst kleine Lecksteine angebracht werden, die als Einzelgaben in kurzer Zeit verzehrt sind. Entsprechend würden für vollständige Behandlungen Packungen mit einer der Behandlung entsprechenden Anzahl von kleinen Lecksteinen bereitgestellt, so dass diese in den richtigen zeitlichen Abständen dem Tier vorgesetzt werden können.

Die Lecksteine werden vorzugsweise luftdicht verpackt. Dadurch wird eine Verflüchtigung von Heilstoffen, insbesond re von ätherischen Ölen, verhindert. Um keine unnöti-

gen Verpackungsabfälle zu erzeugen, werden vorzugsweise fressbare Verpackungsmaterialien verwendet.

Patentansprüche

1. Leckstein (1) **gekennzeichnet durch** eine feste Grundmasse, die von Säugetieren durch Lecken abtragbar ist und durch mindestens einen der Grundmasse zugegebenen Zusatz zum Lindern von Beschwerden.

2. Leckstein nach Anspruch 1, dadurch gekennzeichnet, dass mindestens ein Zusatz hustenlindernd und/oder schnupfenlindernd ist und dabei vorzugsweise zumindest ein ätherisches Öl, wie insbesondere Eucalyptusöl oder Pfefferminzöl, und/oder Kräutersubstanz mindestens einer Heilpflanze umfasst.

3. Leckstein nach Anspruch 2, dadurch gekennzeichnet, dass ätherisches Öl mit einem Gewichtsanteil von 0.1 - 10 Gew.% des gesamten Lecksteines zugesetzt ist, wobei vorzugsweise eine Mischung aus ätherischen Ölen eingesetzt wird, welche Ölmischung insbesondere aus 25 Gew.% Eucalyptusöl, 50 Gew.% Pfefferminzöl, 10 Gew.% Thymianöl, 5 Gew.% Anisöl und 10 Gew.% Fichtennadelöl besteht, wobei einzelne Öle weggelassen und die verschiedenen Anteile um bis zu 20 Gew.% geändert werden können.

4. Leckstein nach Anspruch 1, dadurch gekennzeichnet, dass dieser mindestens einen Magen-, Leber- und/oder Gallebeschwerden lindernden Zusatz, vorzugsweise mit mindestens einen Wirkstoff aus Pfefferminze, Wermut, Kümmel, Fenchel und/oder Tausendgüldenkraut umfasst, wobei der mindestens eine Wirkstoff in der Form von Pflanzenteilen, vorzugsweise in der Form einer Kräutermischung, mit Anteilen der einzelnen Pflanzen von 0.5 bis 10, insbesondere von 1 bis 5 Gew.% des Lecksteingewichtes und/oder in der Form von ätherischen Ölen mit einem Öl-Gesamtanteil von 0.1 bis 10 Gew.% des Lecksteines vorliegt.

5. Leckstein nach Anspruch 1, dadurch gekennzeichnet, dass mindestens ein Zusatz Beschwerden der Pansenacidose mindert und dabei vorzugsweise basische Zusatzstoffe, wie Natriumbikarbonat, Magnesiumoxid und/oder Calciumkarbonat umfasst, wobei der Gesamtanteil der basischen Komponenten bis nahe an 100 Gew.% gehen kann.

6. Leckstein nach Anspruch 1, dadurch gekennzeichnet, dass mindestens ein Zusatz blähungslindernd ist, wobei dieser Zusatz gegebenenfalls Fenchelöl und/oder Kümmelöl mit Anteilen im Bereich von 1 bis 5, vorzugsweise von im wesentlichen je 2 Gew.% und insbesondere ein schaumbrechendes Mittel bzw. ein Tensid mit einem Anteil von 1 bis 10 vorzugsweise im wesentlichen von 6 Gew.% umfasst.

7. Leckstein nach Anspruch 1, dadurch gekennzeichnet, dass mindestens ein Zusatz Nieren- und/oder Blasenbeschwerden, insbesondere Harnwegsentzündungen, lindert und dabei vorzugsweise einen Wirkstoff aus Brenessel und/oder Wacholder, insbesondere in der Form von Wacholderöl und Brenesselextrakt umfasst, wobei beide Anteile im Bereich von 1 bis 10 Gew.%, vorzugsweise bei im wesentlichen bei 5 Gew.% liegen.

8. Leckstein nach Anspruch 1, dadurch gekennzeichnet, dass mindestens ein Zusatz Parasitenbefall insbesondere Eingeweide-Wurmbefall lindernd ist und dabei vorzugsweise Piperazin und/oder mindestens einen Wirkstoff des Farnkrautes umfasst, wobei der Anteil des Zusatzes zwischen 2 und 20, vorzugsweise bei im wesentlichen 10 Gew.% liegt.

9. Leckstein nach Anspruch 1, dadurch gekennzeichnet, dass mindestens ein Zusatz zum Lindern von Milchfieber-Beschwerden, bzw. Metritis, Mastitis und/oder Agalaktie zugegeben ist, welcher einen natürlichen oder künstlichen antimikrobiellen Wirkstoff, beispielsweise Zinkbacitracin in einem Anteil von 1 bis 5, vorzugsweise von im wesentlichen 2 Gew.% umfasst.

10. Leckstein nach Anspruch 1, dadurch gekennzeichnet, dass mindestens ein Zusatz Insektenbefall-Beschwerden lindert, indem der Befall aufgrund einer vom Zusatz ausgehenden Ausdünstung reduziert ist, wobei der Zusatz vorzugsweise Knoblauch in der Form von Knoblauchpulver mit einem Anteil von 2 bis 15, vorzugsweise von im wesentlichen 10 Gew.% oder Knoblauchöl mit einem Anteil von 0.1 bis 4, vorzugsweise von im wesentlichen 1 Gew.% umfasst.

11. Leckstein nach Anspruch 1, dadurch gekennzeichnet, dass mindestens ein Zusatz stresslindernd ist und dabei vorzugsweise Baldrian umfasst , wobei gemahlene

Baldrianwurzeln, vorzugsweise mit einem Anteil von 1 bis 10 Gew.% und/oder Baldriantrockenextrat mit einem Anteil von 1 bis 5, insbesondere von 2 Gew.% zugegeben ist.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CH 98/00166

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 : A23K1/175
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 : A23K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 178 982 A (MERCK & CO. INC.), 28 January 1970 (28.01.70) ; See page 2, left hand column, lines 23-28, lines 49-61, page 3, example 1.	1.8
X	EP 0 218 051 C (BUSCH MANFRED), 15 April 1997 (15.04.97) ; See page 2, lines 28-32 and also claims 1-3.	1.2.4
X	EP 0 180 539 A (CIBA GEIGY AG), 07 May 1986 (07.05.86) ; See page 15 *Second paragraph and on page 42, second paragraph*.	1
X	US 4 904 486 A (DONOVAN DENNIS ET AL), 27 February 1990 (27.02.90) ; See the abstract, column 2, lines 35-45.	1,5
X	DE 33 24 645 A (AUSSEER SALZ MINERAL FUTTER), 01 March 1984 (01.03.84) ; *See page 2, last paragraph and page 3, the last paragraph with page 4, first line*.	1,5
X	US 4 171 386 A (DICKERSON CHARLES W ET AL), 16 October 1979 (16.10.79) ; See the abstract, column 6, example 3*.	1,5

☐ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
15 January 1999 (15.01.99)	22 January 1999 (22.01.99)
Name and mailing address of the ISA/ European Patent Office.	Authorized officer Stoltner, A Telephone No

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CH 98/00166

Patent document cited in search report	Publication date	Patent familiy member(s)	Publication date
GB 1178982 A	28-01-1970	NONE	
EP 218051 C	15-04-1987	DE 3532363 A	12-03-1987
		CA 1272446 A	07-08-1990
		DK 431686 A	12-03-1987
		FI 863618 A	12-03-1987
EP 0180539 A	07-05-1986	AU 4752785 A	27-03-1986
		DK 420785 A	19-03-1986
		JP 61085390 A	30-04-1986
US 4904486 A	27-02-1990	US 4562077 A	31-12-1985
		AU 561032 B	30-04-1987
		AU 2180783 A	26-04-1985
		EP 0141878 A	22-05-1985
		US 4708877 A	24-11-1987
DE 3324645 A	01-03-1984	AT 374343 B	10-04-1984
		AT 88683 A	15-07-1984
		AT 324982 A	15-09-1983
US 4171386 A	16-10-1979	FR 2421562 A	02-11-1979
		US RE31804 E	15-01-1985

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/CH 98/00166

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES

IPC 6 A23K1/175

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IPC 6 A23K

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C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	GB 1 178 982 A (MERCK & CO. INC.) 28 January 1970 *siehe Seite 2, linke Spalte, Zeilen 23-28, Zeilen 49-61, Seite 3, Beispiel 1* ---	1,8
X	EP 0 218 051 C (BUSCH MANFRED) 15 April 1997 *siehe Seite 2, Zeilen 28-32 sowie Ansprüche 1-3* ---	1,2,4
X	EP 0 180 539 A (CIBA GEIGY AG) 7 May 1986 *siehe Seite 15, 2ter Absatz und auf Seite 42, 2ter Absatz* ---	1

☐ Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

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INTERNATIONALER RECHERCHENBERICHT

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C (Fortsetzung). ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	US 4 904 486 A (DONOVAN DENNIS ET AL) 27 February 1990 *siehe Zusammenfassung, Spalte 2, Zeilen 35-45*	1,5
X	DE 33 24 645 A (AUSSEER SALZ MINERAL FUTTER) 1 March 1984 *siehe auf Seite 2, 1ster Absatz und Seite 3, letzter Absatz mit Seite 4, erste Zeile* ---	1,5
X	US 4 171 386 A (DICKERSON CHARLES W ET AL) 16 October 1979 *siehe Zusammenfasssung, Spalte 6, Beispiel 3* -----	1,5

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen
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Im Recherchenbericht angeführtes Patentdokument		Datum der Veröffentlichung	Mitglied(er) der Patentfamilie			Datum der Veröffentlichung
GB 1178982	A	28-01-1970	KEINE			
EP 218051	C	15-04-1987	DE	3532363	A	12-03-1987
			CA	1272446	A	07-08-1990
			DK	431686	A	12-03-1987
			FI	863618	A	12-03-1987
EP 0180539	A	07-05-1986	AU	4752785	A	27-03-1986
			DK	420785	A	19-03-1986
			JP	61085390	A	30-04-1986
US 4904486	A	27-02-1990	US	4562077	A	31-12-1985
			AU	561032	B	30-04-1987
			AU	2180783	A	26-04-1985
			EP	0141878	A	22-05-1985
			US	4708877	A	24-11-1987
DE 3324645	A	01-03-1984	AT	374343	B	10-04-1984
			AT	88683	A	15-07-1984
			AT	324982	A	15-09-1983
US 4171386	A	16-10-1979	FR	2421562	A	02-11-1979
			US	RE31804	E	15-01-1985

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INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

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(74) Gemeinsamer Vertreter: SIEMENS AKTIENGESELLSCHAFT; Postfach 22 16 34, D–80506 München (DE).

(81) Bestimmungsstaaten: CN, US, europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

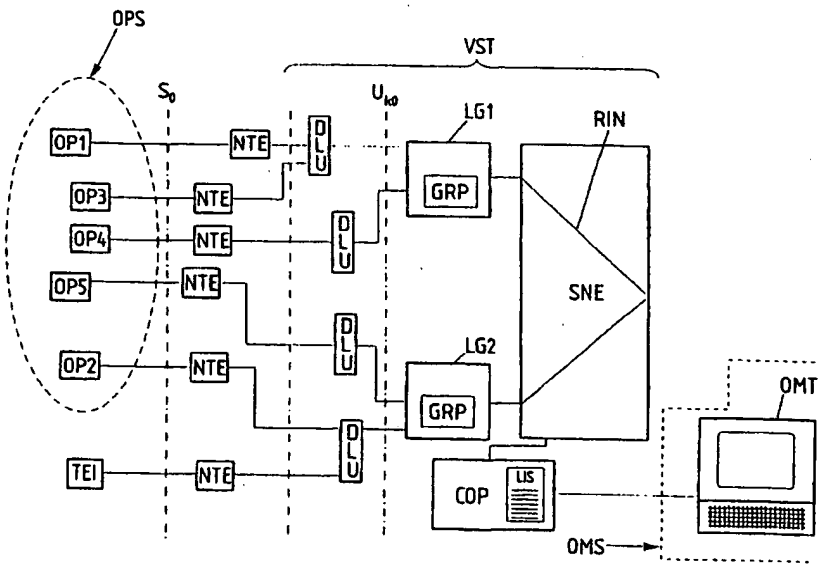
Veröffentlicht
Mit internationalem Recherchenbericht.
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist; Veröffentlichung wird wiederholt falls Änderungen eintreffen.

(54) Title: METHOD FOR TRANSMITTING DATA BETWEEN MEMBERS OF AN OPERATOR SERVICE

(54) Bezeichnung: VERFAHREN ZUM ÜBERTRAGEN VON DATEN ZWISCHEN MITGLIEDERN EINES OPERATORSERVICE

(57) Abstract

The invention relates to a method for transmitting data between members (OP 1, ..., OP 5) of an operator service (OPS) in a digital telecommunications network (NET) in which a calling operator (OP1) sends, to the switching center (VST) thereof, a request together with the identification of a called operator and at least one first data set. A request for the disclosure of information concerning the position of the called operator (OP 2) is sent from the group processor (GRP) of the connection group (LG1) to the coordination processor (COP). Said coordination processor determines the information concerning position from a list (LIS) and sends this information to the group processor (GRP) of the calling operator (OP 1). The group processor establishes a data connection via a data interface (RIN). The first data set is sent over a data channel to the called operator (OP 2), and the connection is then established in the data channel up to the calling operator.



(57) Zusammenfassung

Ein Verfahren zum Übertragen von Daten zwischen Mitgliedern (OP 1, ..., OP 5) eines Operatorservice (OPS) in einem digitalen Telekommunikationsnetz (NET), bei welchem ein rufender Operator (OP 1) an seine Vermittlungsstelle (VST) eine Aufforderung samt der Identifikation eines gerufenen Operators und zumindest einem ersten Datensatz sendet, von dem Gruppenprozessor (GRP) der Anschlußgruppe (LG 1) eine Aufforderung zur Bekanntgabe von Lageinformationen bezüglich des gerufenen Operators (OP 2) zu dem Koordinationsprozessor (COP) gesandt wird, dieser die Lageinformation aus einer Liste (LIS) ermittelt und zu dem Gruppenprozessor (GRP) des rufenden Operators (OP 1) sendet, dieser Gruppenprozessor über eine Datenschnittstelle (RIN) eine Datenverbindung aufbaut, der erste Datensatz über einen Datenkanal zu dem gerufenen Operator (OP 2) gesandt wird, und sodann die Verbindung in dem Datenkanal bis zu dem rufenden Operator aufgebaut wird.

LEDIGLICH ZUR INFORMATION

Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

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